OTC MEDICAL OFFICER'S REVIEW

NDA#: 21-213
Drug Name: Lovastatin 10 mg
Sponsor: Merck & Co., Inc. and Johnson & Johnson ◦ Merck Consumer Pharmaceuticals Co.
Pharmacologic Category: Cholesterol Lowering Drug
Proposed Indication: To Lower Cholesterol
Dosage Form/Route of Administration: Tablet/Oral
Submission Date: 12/10/99
Review Date: 6/5/00
Reviewer Name: Andrea Leonard-Segal, M.D., M.S.
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Material Reviewed:
Data from 7 clinical studies are included in this application: 4 in-home "Use" studies (Protocols 076, 077, 079, 081); 1 placebo-controlled double-blind efficacy study (Protocol 075); and 2 pharmacokinetic studies (Protocols 078 and 082). In addition, 3 label comprehension studies are provided as References 199, 200, and 201. This document is a review of the 4 actual use studies. The label comprehension studies will be reviewed in conjunction with the Division of Drug Marketing, Advertising, and Communication.

Background:
Lovastatin has been available by prescription in the United States since 1987 for the reduction of elevated total cholesterol (TC) and low density lipoprotein (LDL) cholesterol levels in patients with primary hypercholesterolemia when the response to a cholesterol-lowering diet, and to other non-pharmacological measures alone is inadequate. Lovastatin 10 mg/day is being proposed by the sponsor as a nonprescription adjunct to diet and exercise for treatment of otherwise healthy adults without heart disease who have a total cholesterol (TC) $\leq$ 240 mg/dl and a low density lipoprotein cholesterol (LDL) $\geq$130 mg/dl.

Data from 3 efficacy trials (075, 016, and 061), were reviewed by another FDA medical reviewer. The mean percent reduction of LDL in the 12-week 075 trial was 17.5%, at 6 weeks in trial 016 was 21.3% and at 12 weeks in trial 061 was 15.2%. HDL values increased 4.5% in 016, 7.2% in 061 and 6.5% in 075. These trials demonstrated that lovastatin 10 mg lowers LDL cholesterol and raises HDL in populations of subjects with the cholesterol profile of those in this actual use trial.

Protocol 076 – A Multicenter, Open-Label Study to Evaluate Compliance and Persistence in Patients Who Self-Select to Receive Lovastatin 10 mg for Treatment of Moderate Primary Hypercholesterolemia (Total Cholesterol 200 - 240 mg/dl) in a Pharmacy Setting.

Purpose:
The purpose of this study was to determine the efficacy of lovastatin 10 mg to treat Total Cholesterol 200-400 mg/dl in an actual use setting. The self-selection behavior of subjects, persistence and compliance with the medication, and adverse events were to be studied.

Investigators:
Fifty-nine retail pharmacy study sites and one toll-free number physician consultation center in the United States participated in this study.

Comment: The physician investigator was a board-certified internist and gastroenterologist. The other investigators were licensed pharmacists located throughout the United States.

Objectives:

The primary objectives of this study were to:

1. Evaluate the mean reduction in LDL cholesterol at the first follow-up visit (Visit 2).
2. Evaluate the mean reduction in LDL cholesterol in subjects remaining on lovastatin 10 mg at 6 months.

The secondary objectives of this study were to:

1. Evaluate the ability of study participants to correctly self-select whether to take lovastatin 10 mg as per the labeling.
2. Evaluate the ability of patients to remain on lovastatin 10 mg in the over-the-counter (OTC) setting over the 6-month (24-week) study period.
3. Evaluate the tolerability of lovastatin 10 mg as measured by the incidence of clinical adverse experiences.

Patient Selection:

1. Inclusion Criteria:
   a. Men 45 years or older/women 55 years or older without heart disease (e.g., heart attack or angina).
   b. After a trial of a low-fat diet to lower cholesterol within the previous year total cholesterol measured on Day 1 had to be 200-240 mg/dl, and LDL cholesterol had to be ≥130 mg/dl. Individuals may have met all other criteria, but if they had not tried a low-fat diet to lower cholesterol within the year prior to Visit 1, they were not eligible to participate in the study.
   c. Subjects had to be in general good health and not have any debilitating disease.
   d. Subjects had to demonstrate a willingness to participate in the study as evidenced by written informed consent.
   e. Patients had to be able to comprehend and comply with the study requirements.

Comment: There were no criteria to determine if subjects had actually tried a low fat diet or "just thought" they were reducing fat intake, or how long they tried dietary modification, or if they understand what foods are high in fat and what foods are not.

The sponsor states that the last 3 inclusion criteria were required for entry into the study but are not part of the proposed nonprescription lovastatin treatment paradigm, and that therefore they were not listed on the prototype market package label used in the study.

Comment: If subjects had to be in general good health and not have any debilitating disease, then the safety data may be not be predictive for the OTC population.

2. Exclusion Criteria (The sponsor states that all of the exclusion criteria below were listed on the prototype market package label used in this study, except where otherwise noted.)
   a. Current or recent (within the 2 months prior to Visit 1) participation in any drug study. (Note: This was a study-specific exclusion, which was not listed on the prototype market package label used in this study.)
   b. Any contraindication to the use of lovastatin, including allergy to prescription Mevacor (lovastatin), diagnosis of hepatitis, or a past history of liver disease.

c. Patients who were currently taking cyclosporine, itraconazole, ketoconazole (or other systemic azole antifungal medications), erythromycin, clarithromycin, nefazodone, oral corticosteroids, or mibefradil dihydrochloride. (The sponsor states that ketoconazole, mibefradil dihydrochloride, and oral corticosteroids were not listed on the prototype market package label. Ketoconazole and mibefradil dihydrochloride were added to the protocol as safety risk exclusions after the product cartons were printed. The sponsor states that oral corticosteroids were a "study-specific" exclusion because of their potential to elevate serum cholesterol levels.
d. Patients who were taking any other cholesterol-lowering medication (including OTC niacin in doses > 500 mg/day) within 4 weeks prior to the screening visit (Day 1).
e. Women of childbearing potential, pregnant women, or women who were breast-feeding.
f. History of heart disease or peripheral vascular disease.
g. History of familial premature heart disease (heart attack before age 55 in parents or siblings).
h. Consumption of 3 or more alcohol-containing drinks per day on most days of the week.

Comments:
The presence of peripheral vascular disease is not mentioned on the study label. It is unclear why the sponsor left stroke or TIA out of the exclusion criteria.

The exclusion criteria discuss other cholesterol improving treatments. Estrogen replacement therapy not mentioned. In the efficacy trial, 075, hormone replacement therapy was permitted only if a woman had been on a stable dose for 1 month. The exclusion criteria, and the study label omitted some drugs that might interact with lovastatin (protease inhibitors, coumarin anticoagulants).

Study Design:
This was an open-label, uncontrolled, multicenter study at pharmacies that were equipped with CHOLESTECH L·D·X™ (Cholestech Corporation) desktop fingerstick cholesterol analyzers. Study sites were staffed by Pharmacist Co-Investigators who for took all measurements, assessed eligibility, and collected and recorded all study data. There were 4 pharmacy study-site visits, each approximately 8 weeks apart, for a study duration of approximately 24 weeks.

The study was advertised in print, radio, and television media, using common advertising copy to attract the target population. The sponsor states that advertising efforts were made to attract a large number of minorities and that some sites were selected because they had a high population of African-Americans, Hispanics, or Native Americans.

Comment: The print, radio and television advertisements were misleading; they only discussed total cholesterol. For example, subjects read, "Numerous studies have shown that a total cholesterol level above 200 mg/dl can increase your risk of developing heart

disease." The television commercial also misled consumers by referring to cholesterol over 200 mg/dl as being "high," instead of "borderline."

One radio ad was in Spanish. It is unclear why the sponsor did this because a prerequisite of the study (and Protocols 077, 079, and 081) was that subjects understand English.

Interested individuals were directed via a toll-free scheduling service to the participating pharmacy closest to them. At the study site, participants were shown a prototype market package label developed for this study and were asked to make a self-selection decision by answering the following 2 questions:

1. "After reading all of the information on the product carton label, and knowing your current health situation, do you feel this product is right for you?"
a) Yes
b) No
c) I need more information

2. "If this product were available for you to use right now, what would you decide to do next?"
a) Obtain this product and use it
b) Get my cholesterol checked before deciding to use this product
c) Talk to a doctor before deciding to use this product
d) Get my cholesterol checked and talk to a doctor
e) Would not be interested in using this product

The participants also completed a self-administration medical history questionnaire that consisted of the study inclusion/exclusion criteria. The Pharmacist Co-Investigators evaluated all of the responses and determined whether or not participants were potentially qualified to receive study medication. Participants were potentially qualified if:
1. they indicated either that the product use was right for them or that they needed more information
2. they met all of the inclusion criteria and none of the exclusion criteria
3. they provided written informed consent.

Comment: The informed consent emphasized that the study investigator pharmacist would inform subjects of all known risks of the product. In bold print, it told subjects that they could call the toll-free number if they needed to talk to a study doctor. The study made access to information from a health care professional much easier for a participant than it might actually be for a consumer if this product were sold over-the-counter. This situation does not mimic an "actual use" setting and biases the study participants toward making sure they are self-selecting properly.

The informed consent also listed ketoconazole and oral corticosteroids (not on the product label), but not all other drugs that might present similar risks. The informed consent made special mention about the unknown risks of lovastatin in pregnancy and about not taking this product with other cholesterol lowering drugs, therefore,

emphasizing risks more than would be expected from most OTC products. Those who refused to sign the informed consent may have done so because they learned of risks from that document that may not have been specifically mentioned in the label.

Neither the study label nor the informed consent form warn about use with coumarin anticoagulants, despite the fact that, for the prescription drug, a baseline prothrombin time is recommended and should be repeated frequently enough during early therapy to ensure that no significant alteration occurs.

The self-administered medical history form does not ask subjects to list the drugs that they are presently taking, so all we know is whether subjects thought they were taking the listed contraindicated drugs. Such a question may have clarified whether subjects actually understood which drugs are contraindicated.

The informed consent section on "Prior Experience with Drug" is misleading. It tells the subject, "Research studies have also shown the MEVACOR® was effective in slowing the development of fat build-up (atherosclerosis) in middle-aged men with coronary heart disease." It does not mention that this has not been demonstrated for subjects who meet the entry conditions for this study and are taking lovastatin 10 mg.

Potential qualification was not determined by the self-reported cholesterol values but instead was determined by a cholesterol test done at the pharmacy. The sponsor states that to reduce the number of uncalculated LDL cholesterol values due to high triglycerides, all participants were instructed that they should not eat a meal within 2 hours of their fingerstick lipid profiles. Those with total cholesterol 200-240 mg/dl and LDL cholesterol 130 mg/dl were fully qualified for study drug. Participants who consumed a meal within 2 hours were instructed to return to the site later that same day so the fasting requirement could be met.

Participants with total cholesterol 190-199, or 241-250 mg/dl or with LDL 120-129 were permitted to return to the study site to have their cholesterol re-tested. Although not stated in the protocol, participants whose LDL cholesterol could not be calculated by the cholesterol analyzer could also be re-tested if deemed appropriate by the Study Physician Co-Investigator. The maximum number of re-tests a participant could receive was 2.

Comment: The criteria would probably admit subjects with a baseline cholesterol less than 200 who may have had a high cholesterol meal 2 hours earlier. In addition, it may have also allowed for individuals with total cholesterol >240 mg/dl to participate since they could have had a random cholesterol <240 mg/dl at one screening.

Qualified subjects were given 2 blister packs (56 tablets total) of lovastatin 10 mg packaged in product cartons bearing the prototype market package label. They were expected to use the product according to their understanding of the indications, warnings and directions in the product label, and were directed via the label to take 1 tablet of study medication daily with the evening meal. Each blister card was imprinted with the days of the week and week numbers 1 through 4. There was 1 blister card per carton.

Each carton of study drug also contained a patient package insert, an informational brochure, daily-dosing reminder stickers, and a compliance program enrollment card. Subjects who enrolled in the compliance program were provided with a cookbook and monthly newsletters containing educational and compliance-promoting information related to the study drug, diet, and exercise. They were also provided with "Patient Information Cards" that included their current total and LDL cholesterol values, the days/times when cholesterol testing was available at the pharmacy and the toll-free telephone number for the Study Physician Co-Investigator.

Comment: It appears that subjects had to call a toll free number or mail a card to receive the American Heart Association Cookbook. They also received a subscription to "The Passport to Healthy Living" newsletters with information about lowering cholesterol, eating healthy, recipes, exercise, and maintaining a healthy lifestyle. If subjects received all of the above information, it is possible that their cholesterol values decreased during the study, as a result of better dietary compliance. This would confound the efficacy data regarding the study medication. There was no formal diet program as a lead-in to this study.

The Study Physician Co-Investigator was to answer any questions and receive reports of adverse experiences. With regard to calls from participants concerning their qualification for study drug, the Study Physician Co-Investigator would review the patient's medical history and confirm the subject's qualification for the study based on all inclusion/exclusion criteria. If it was determined that someone was not qualified, he/she was instructed to discontinue from the study and return all study medication to the study pharmacy. (See **Figure 076-1**.)

Subjects were instructed to return for additional supplies of study drug as needed. Since study drug was provided in quantities sufficient for 8 weeks of treatment, the follow-up visits were estimated to occur at approximately Week 8 and Week 16. However, because subjects were not given appointments to return for follow-up Visits 2 and 3, the timing of those visits was dependent on when individuals returned for more study drug. All were scheduled to return for the end-of-study visit (Visit 4) 8 weeks after Visit 3 or 24 weeks after Visit 1, whichever was the shorter interval.

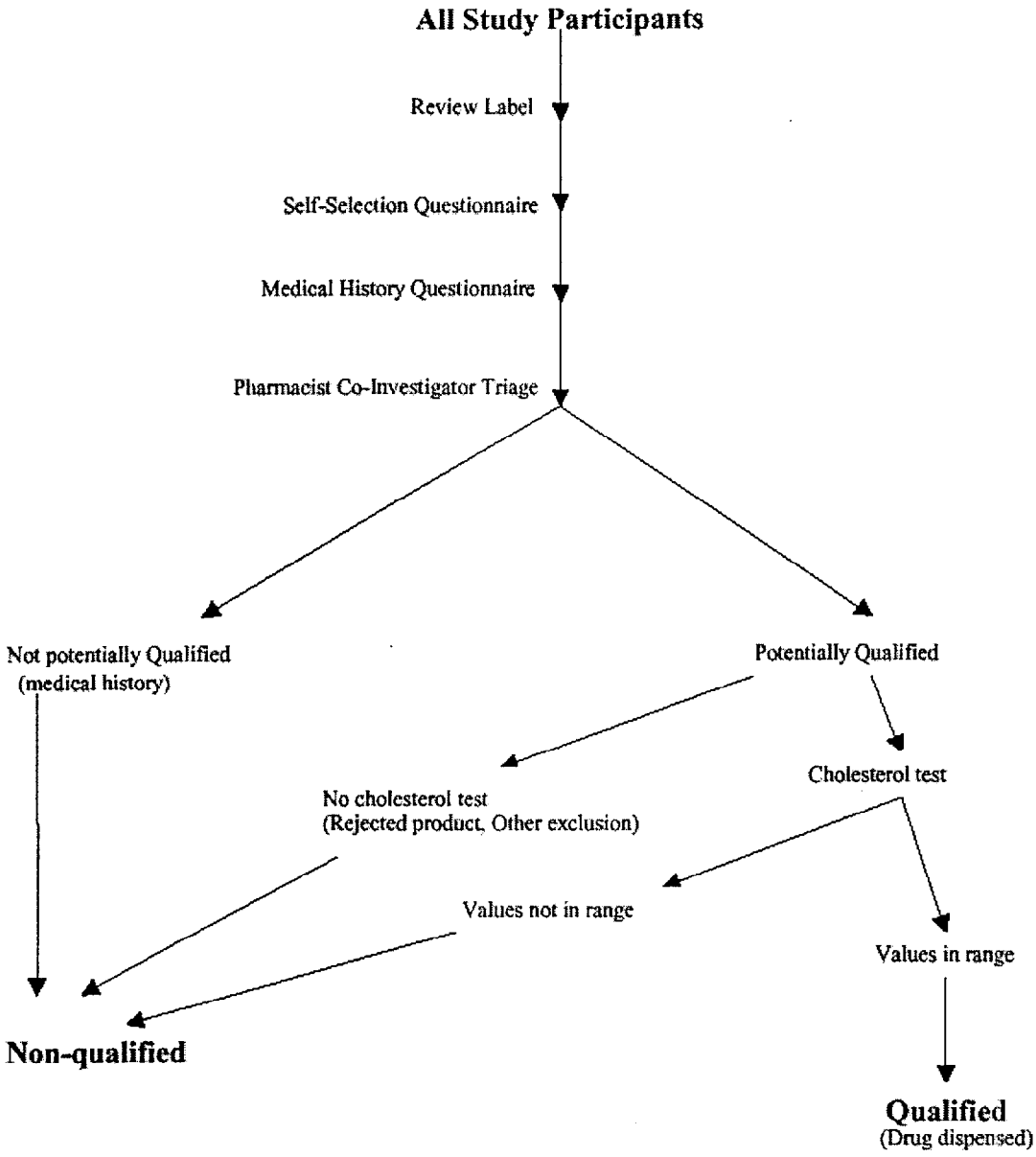
At each study visit:

1. The subject returned unused drug and all blister packs and cartons, and the Pharmacist Co-Investigator counted and recorded the returned tablets.
2. Unsolicited clinical adverse experience information was collected at each study visit by the pharmacist (and at any time during the study by the toll-free number physician).
3. A lipid profile was done and the total and LDL cholesterol values were recorded onto the Patient Information Card.
4. A new 8-week supply of study drug was dispensed (except for the last visit).

Subjects for whom the LDL-cholesterol level had not decreased by the Week 8 measurement, were advised to have a cholesterol retest. The confirmatory cholesterol

test was to be done within a few days. If the additional measurement still did not show a reduction in LDL cholesterol, the subject could consult with the Study Physician Co-Investigator regarding the appropriateness of continuing study drug. (See **Figure 076-1**.)

Figure 076-1. Flow Diagram of Study Design



At the end of the primary study period (Visit 4, approximately 6 months), subjects could enroll in 2, 6-month treatment extensions of the protocol, resulting in a maximum possible treatment duration of 18 months. The sponsor states that the treatment extensions are not mentioned in the study protocol because the plans originated after the primary study was initiated. The sponsor states that results from these treatment extensions will be summarized in a separate Clinical Study Report (CSR).

Although not mentioned in the study protocol, those who received study medication were asked to complete a brief self-administered market research questionnaire at the completion of their final visit. The sponsor states that the purpose was to understand subjects' behavior during the study (e.g., dosing patterns, discussions about the study with personal physician, diet, and exercise habits), and their reactions to the fingerstick cholesterol test and the marketing materials. Adverse experience information was collected throughout the clinical study, including at the final visit prior to administration of the market research questionnaire. Since the market research questionnaires were outside of the clinical study, the sponsor states that the data were not reviewed by the study investigators, but were forwarded directly to the market research organization. The sponsor states that because of this, if a study participant spontaneously reported a side effect as part of an answer to a market research question, there was no mechanism for including it in the clinical study database.

Comment: The sponsor should have created a mechanism for the reporting and recording of all adverse experiences into the database.

The schedule of clinical observations, laboratory measurement and study procedures is summarized in **Table 076-1**.

Table 076-1. Summary of Study Visits

	Visit 1 Day 1	Visit 2 Week 8	Visit 3 Week 16	Visit 4 Week 24
Subject read label and completed self-selection decision form	X			
Subject completed medical history form including inclusion /exclusion criteria	X			
Pharmacist reviewed completed forms and determined if subject was potentially qualified for study drug	X			
Informed consent obtained	X			
Lipid profile measured and recorded on case report forms (CRF)	X	X	X	X
Study drug and patient information card dispensed	X	X	X	
Qualification for study drug confirmed by physician (if subject chose to do so by telephone consultation)	X			
Pharmacist collected returned study drug, packaging and accounted for unused drug		X	X	X
Adverse experience information collected from subject in person (at next study visit) or via telephone at any time (by study nurse or physician)		X	X	X

Comment:
The reading ability of consumers interested in participating in the study was not assessed. One question on the "Demographics" form did ask the last level or grade of school completed. No questions assessed how well subjects understood the meaning of their cholesterol profiles.

It would be useful to know if the availability of a study physician influenced whom subjects contacted regarding taking the study medication (i.e. study physician or personal health care provider). If this medication were available OTC, users should be strongly advised to communicate with their personal physicians.

Laboratory Measurements:
Lipid profiles (total cholesterol, LDL, HDL, triglycerides) were done on the CHOLESTECH L·D·X™ desktop analyzer. LDL cholesterol was calculated by the analyzer using the Friedewald Approximation as follows:

LDL = Total Cholesterol – (HDL) – (Triglycerides/5)

The sponsor states that although not addressed in the protocol, the analyzer did not calculate the LDL cholesterol value when triglycerides > 400 mg/dl, or an HDL < 15 or > 100 mg/dl. The study physician co-investigator could authorize a retest in such cases.

Evaluation Criteria:

Efficacy

The cholesterol values considered to be "baseline" were from the Visit 1 cholesterol test (i.e., either the initial test on Day 1, or the last retest). Percent change from baseline in LDL cholesterol at approximately 8 weeks was used to address the main primary hypothesis for efficacy. The other lipid measurements were summarized. The sponsor states that the percent change from baseline in LDL cholesterol at 24 weeks was assessed to show sustained effect in the patients who were still on medication at 6 months.

Persistence, Compliance, Self-Selection

Persistence was summarized at each visit by calculating the number (%) of patients who returned for the visit having taken any tablets of study drug. At each visit, compliance was calculated (in subjects who were still taking the drug) by dividing the number of tablets taken by the number of days the subject had study drug. Accuracy of self-selection and compliance with label instructions to call the study physician were characterized.

Comment: By study definitions, a subject could not be compliant to any degree if he/she was not persistent. However, compliance offers the only clinically meaningful information about whether the drug would actually be used properly in the OTC market.

Safety

The sponsor defined an adverse experience as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a preexisting condition temporally associated with any use of the study drug, whether or not considered related to the use of the product.

1. Clinical Safety – The sponsor states that at each visit, subjects were asked a non-leading question to determine whether they had any adverse experiences. Subjects also had the opportunity to report adverse events at any other time during the study. All adverse events were recorded on the CRF and graded as:
    a. Mild – Awareness of sign or symptom but easily tolerated,
    b. Moderate – Discomfort enough to interfere with usual activity, or
    c. Severe – Incapacitating, with inability to work or do usual activity.

The investigator judged the seriousness of the adverse event, the action taken (with respect to discontinuation from therapy), and whether or not the study drug was responsible for the adverse experience. Possible ratings for assessing drug relationship were:
    a. Definitely not (no relationship)
    b. Probably not (relationship is unlikely)

c. Possibly (relationship may exist)
d. Probably (relationship is likely)
e. Definitely (unquestionable relationship)

Comment: The question that investigators asked subjects to determine whether they had any adverse events is not provided, so it cannot be evaluated as to whether it was leading.

2. Laboratory Safety – There were no laboratory safety measurements in this study.

Comments:
The recommendation for prescription lovastatin is to measure baseline liver function tests (LFTs), and then at 6 and 12 weeks and periodically thereafter. The sponsor did not present data as to whether LFT elevations are a problem with lovastatin 10 mg.

It would be prudent to see whether there are changes in LFTs in this population group, self-selectors not under the supervision of a physician. It would also be prudent to assess what percentage of subjects who think they have normal liver function at entry and actually do not.

CPK measurements in subjects complaining of muscle aches or weakness would have been useful in this study as well, to determine whether these symptoms were secondary to lovastatin.

Statistical Planning and Analysis:
Definitions of Study Participant Subsets:
1. All Study Participants: All individuals who visited the study sites and provided any study data were assigned a patient identification number. These participants responded to the study advertising campaign, reviewed the proposed product label, answered the self-selection questions and participated in the medical history questionnaire with the pharmacist.
2. Participants Likely to Buy (Potential Purchasers): Participants who answered self-selection question #2 as, "Obtain this product and use it" or, "Get my cholesterol checked before deciding to use this product" (without also wanting to talk to a doctor). Participants who answered, "Would not be interested in using this product" or either response that involved talking to a doctor were not in this group.
3. Nonqualified Participants: Subset of all study participants who were disqualified by the pharmacist from receiving study drug for either medical history, cholesterol test results, other inclusion/exclusion criteria. This included participants who made a self-selection decision to reject the product.
   a. Not Potentially Qualified Participants: All nonqualified participants who had 1 or more exclusion criteria from medical history and therefore could not proceed to have a cholesterol test.
   b. Potentially Qualified Participants (Who Eventually Were Nonqualified): Subset of all nonqualified participants who had no medical history exclusions and therefore could proceed to have a cholesterol test performed.

Had a Documented Cholesterol Test: Subset of Potentially Qualified who had a cholesterol test but cholesterol and / or LDL values were outside of protocol-specified ranges.

Did Not Have a Documented Cholesterol Test: Subset of Potentially Qualified Participants who did not have a cholesterol test due to at least one of the following: 1) rejected product, or 2) other inclusion / exclusion criteria (not willing to sign informed consent or could not comprehend or comply with study requirements).

4. Qualified Patients (Potentially Qualified Participants Who Became Qualified) Subset who were potentially qualified based on medical history, who signed informed consent, had the cholesterol test and values met study ranges, and were dispensed study drug.

Comment: The sponsor referred to participants in this actual use trial as "patients."

Statistical Hypothesis and Power

The primary hypotheses were:

1. Participants will have a mean reduction in LDL of 14.7% at the week 8 follow-up visit. The sponsor states that this is a satisfactory efficacy outcome in the OTC setting. The study protocol planned to have 660 study participants enrolled (receiving study medication).

2. Participants remaining on lovastatin 10 mg at 6 months will have a mean reduction in LDL cholesterol of 10%.

The secondary hypotheses were:

1. Study participants will correctly self-select use/nonuse of lovastatin 10 mg as per labeling.
2. Most patients will still be on the study drug at 6 months.
3. The study drug will be well-tolerated as measured by incidence of clinical adverse experiences.

Other Measures and Analyses

Persistence with dosing was summarized at each visit by calculating the number (%) of patients who returned for the follow-up visit having taken any of their tablets. Compliance was calculated in the participants who were still on drug at each visit and was defined as the number of tablets taken divided by the number of days the participants had taken study drug in a specified time period. The relationship between efficacy and compliance was explored by summarizing the percent change in LDL cholesterol by compliance level at Visits 2 and 4.

The proportions of study participants who would be likely to buy lovastatin but are ineligible were calculated by comparing the participant's self-selection decision to the eligibility determined by the medical history questionnaire. The eligibility decision made by the pharmacist was compared to the medical history questionnaire and the participant's self-selection and pharmacist decision were also compared.

Demographic information and other subject characteristic data were summarized and were used to assess any association with compliance and persistence. Also the proportion of subjects who contacted the study physician and the proportion that contacted their personal physician were summarized.

Missing Data
The sponsor used 2 approaches for the analysis of efficacy data at Visit 2. For subjects missing LDL values at Visit 2, the baseline LDL was used. The sponsor stated that this approach was conservative since it assumed a missing value came from a participant who did not achieve a reduction in LDL cholesterol from baseline. The second approach was not to include subjects with missing data points in the Visit 2 analysis.

The primary analysis for Visit 4 did not estimate missing data values since the hypothesis was targeted at completers only. Therefore, the analysis of percent change in LDL cholesterol at Visit 4 included only those subjects who had both a Visit 4 LDL measurement and a baseline LDL measurement.

The day ranges for post baseline visits used in the analyses of the lipid and compliance/persistence data are listed in **Table 076-2.** Visit number was defined by relative day ranges, regardless of the actual visit number.

Table 076-2. Week (Day) Ranges for Post-Baseline Visits

	Week (Day) Ranges
Visit 1 (Baseline)	Visit Date ≤ Dispensed Date
Visit 2 (≈ Week 8)	4 Weeks (28 days) < Visit Date ≤ 12 Weeks (84 days)
Visit 3 (≈ Week 16)	12 Weeks (84 days) < Visit Date ≤ 20 Weeks (140 days)
Visit 4 (≈ Week 24)	20 Weeks (140 days) < Visit Date ≤ 28 Weeks (196 days)

Comment: It appears that subjects could have been included in visit data for either Visit 2 or 3 if they returned on day 84 and for either Visit 3 or 4 if they returned on day 140, depending on the number of visits they made. In the data analysis plan, Merck states that if the clinic visit was > 20 weeks it was considered to be Visit 4 regardless of the actual number of visits.

Summary statistics for the efficacy parameters were presented for each measure at Visits 2, 3 and 4. Baseline and percent change from baseline were included. Two-sided 95% confidence intervals were calculated for each mean percent change from baseline at Visits 2, 3 and 4. Exploratory analyses were performed to determine the impact of demographic characteristics on compliance and persistence. Persistence at Visit 4 was defined as a binary outcome (yes or no). A logistic model was used to assess the relationship between persistence and demographics and between compliance and demographics. Self-selection data was evaluated by comparing the subjects' eligibility decisions with the pharmacists', and the eligibility decision made by the pharmacist was compared to that made by the physician when available. Safety information was

summarized. If the incidence of an adverse event was ≥ 5% of enrolled subjects, 95% confidence intervals were provided.

Comment:
In this trial, evaluation of efficacy is impaired by:
1. the absence of a placebo-control,
2. the absence of blinding,
3. 1 baseline cholesterol against which change is measured instead of averaging 2 or 3, and
4. absence of diet monitoring (enrolled subjects were given dietary information along with the drug).

Thus meaningful efficacy information cannot be determined from this trial.

Merck did not summarize safety information for those who actually took the drug. Instead it used the larger denominator of those who received the drug. Thus, the drug-related adverse events would appear to be less frequent than they were, in actuality.

Results:
The "all study participants" group across 59 pharmacy sites had a total of 6095 subjects. Of these 722 (11.8%) were qualified and received study drug and 5373 (88.2%) did not qualify. Of the nonqualified population, there were 3051 potentially qualified participants who had no medical history exclusions as assessed by the Pharmacist Co-Investigator, but who did not receive drug. This group of participants signed the consent form and took a cholesterol test. (**See Table 076-3.**)

Table 076-3. Qualification Status of All Study Participants (N = 6095)

	N (%)
Nonqualifiers	5373 (88.2)
Not Potentially Qualified	2320 (43.2)
Potentially Qualified	3051 (56.8)
Had a documented cholesterol test	2812 (92.2)
Did not have a documented test	239 (7.8)
Excluded due to inability to comply or rejected product	200 (7.1)
Excluded no documented test results	11 (0.4)
Unable to obtain cholesterol values	11 (0.4)
Withdrew consent	7 (0.2)
Other	10 (0.4)
Qualifiers	722 (11.8)

Comments:
Two subjects did not have a Pharmacist Co-Investigator evaluation, and thus, it could not be determined if they were potentially qualified or not potentially qualified. They are not included in the number of subjects in either of these groups. Fourteen patients in the not potentially qualified group had a cholesterol test done in error. They are not included in the count of 2812, those who had a documented cholesterol test. The total

number of subjects who had a cholesterol test performed (not in error) was 3534. The 722 qualifiers constituted 20.4 % of this group.

It is of concern for an OTC setting that of the subjects who expressed an interest in taking this medication only 722 (11.8%) qualified for the study.

Nine hundred eighty-one subjects answered "Yes" to "obtain this product and use it" (question 2 of the self-selection form). Of that 981, 76 indicated that they needed more information and 4 checked lovastatin was not right for them (question 1 of the self-selection form). Only 119 (12.1%) of the 981 subjects were eventually treated with study drug. Without an intermediary, i.e., the pharmacist or physician, it may be that many subjects would take the medication who should not.

Eleven participants were screened twice, at separate times, and assigned different patient identification numbers. Nine of these failed to qualify for study drug on both screening attempts. Two participants failed to qualify on the first screening attempt but qualified and received study drug on the second attempt. The total number of study participants, 6095, includes participant data from both screenings of each of the above 11 participants, but the total of unique individuals who contributed data to the study is 6084. The sponsor states that throughout the report each of the 11 duplicate participants were counted as 2 separate individuals.

There were 60 sites that contributed to the "all study participants" population. One site had only 1 participant and that subject was "nonqualified." Among the other 59 sites, the number of "all study participants" ranged from 26 to 220. The number of qualified subjects from any particular site ranged from 1 to 36.

Among the qualified subjects, 189 (26%) were female and 533 (73.8%) were male. Among the nonqualified subjects 2460 (45.8%) were female and 2883 (53.7%) were male. **(See Table 076-4)** Of the males who had a documented cholesterol test, a higher proportion (26.4%) qualified for study drug compared to females (12.5%).

Comment: These percentages for each gender were of the sum of the potentially qualified participants who had a documented cholesterol test but did not qualify, plus the potentially qualified participants who had a documented cholesterol test and went on to qualify.

Table 076-4. Qualification by Gender (Total Study Participants with Gender Information Collected = 6065)

	Female - N (%)	Male - N (%)
Nonqualifiers	2460 (92.9)	2883 (84.3)
Not potentially qualified	1020 (41.5)	1300 (45.1)
Potentially qualified	1440 (58.5)	1583 (54.9)
Had a documented cholesterol test (percent of potentially qualified)	1326 (92.1)	1486 (93.9)
Did not have a documented test (percent of potentially qualified)	114 (7.9)	97 (6.1)
Qualifiers	189 (7.1)	533 (15.6)

Comment: Thirty subjects did not give information as to their gender and were not included in the gender calculations.

A higher proportion of females (87.5%) who had a documented cholesterol test were excluded for cholesterol test results than males (73.6%). All other patient categories appeared similar between genders.

The mean and median age in both the nonqualified and qualified populations was 60. Five thousand five hundred fifty-three (91%) study participants were Caucasian. A broad range of income groups were represented in both the qualified and nonqualified groups. There were 548 (75.9%) qualified subjects with greater more than a high school education; the relative numbers were slightly lower for the nonqualfiers 3666 (68.2%).

Females were slightly older in both the qualified and nonqualified groups; the mean ages were 62 and 63 respectively for females compared to 58 and 57 for males.

Comment: That females were older than males in this study is not surprising since women could not qualify until they were age 55 but males qualified from age 45.

There were 3548 potentially qualified subjects with baseline cholesterol tests taken. The mean baseline values for LDL cholesterol and total cholesterol were lower in the qualified group than in the nonqualified group. The sponsor states that this indicates that more participants were disqualified for lipids above the study range than below the study range. Mean baseline values for HDL were lower in qualified participants compared to nonqualified participants. **(See Table 076-5.)**

Table 076-5. Baseline Lipid Summary Statistics (All 3548 participants with baseline cholesterol)

	Qualified (N = 722)	Nonqualified (N = 2826)
LDL Cholesterol (mg/dl)		
Number of Subjects	720	2439
Mean LDL	148.2	167.6
Range	98-192	38-367
Total Cholesterol (mg/dl)		
Number of Subjects	722	2825
Mean Total Cholesterol	226.0	267.7
Range	199-266	100-500
HDL Cholesterol (mg/dl)		
Number of Subjects	721	2716
Mean HDL	43.6	52.5
Range	13-88	6-99
Total/HDL Cholesterol		
Number of Subjects	721	2716
Mean ratio	5.7	5.8
Range	2.4-17.9	1.9-45.3
Triglycerides (mg/dl)		
Number of Subjects	722	2798
Mean Triglycerides	172.6	246.0
Range	47-650	45-675

Comment: The table above is taken from Sponsor's Table 6.

The 3548 number of participants at baseline includes the 14 subjects who had the test performed but should not have. Two subjects did not have a baseline LDL. One did not have a baseline HDL. The sponsor notes that 1 study participant at site 51 with a total baseline cholesterol of 266 mg/dl inappropriately received study drug. The range of LDL and total cholesterol values indicates that there were more than this subject in the "qualified" group who did not meet the entry criteria based on cholesterol values and should not have been considered to be qualified.

The proportion of women who fell within the total cholesterol range for the study (200 – 240 mg/dl) was 387 (28.3%) of 1366 compared to 687 (38.3%) of 1793 men.

Comment: Women tended to have higher HDL cholesterol than men in both qualified and nonqualified groups.

Five hundred twenty-three (42.4%) subjects completed the study. The most common reason for discontinuing the study was due to an adverse experience (9.4%). There were 20 (2.8%) subjects who discontinued due to the advice of their personal physician and 14 (1.9%) who did not return for their final visit (i.e., returned their drug packaging by mail). Nine (1.2%) subjects were discontinued because of investigator error. In these cases, subjects were dispensed study drug in error even though they were not eligible for the

study based on medical history or out-of-range cholesterol values; other subjects were inappropriately discontinued due to noncompliance with drug and were also given "investigator error" as a final study status. (**See Table 076-6.**)

Table 076-6. Subjects Who Received Study Medication (N = 722)

	N (%)
Completed Study	523 (72.4)
Discontinued Study	199 (27.6)
Clinical adverse experience	68 (9.4)
Withdrew consent	44 (6.1)
Lost to follow-up	29 (4.0)
Personal physician advised discontinuing	20 (2.8)
Subject did not return for final visit	14 (1.9)
Investigator error	9 (1.2)
Moved	5 (<1)
Lack of response	4 (<1)
Subject failed to complete final visit procedures	3 (<1)
Study physician medical reason	1 (<1)
Physician administered medical history	1 (<1)
Protocol deviation	1 (<1)

Of the 722 qualified subjects on study drug, 213 (30%) reported they spoke to their own personal physician between Visits 1 and 2. Of those 213 subjects, 71 (33%) spoke with their personal physician before they started to take the drug. Nine of the 722 qualified subjects (1.2%) called the study physician to confirm eligibility. One hundred thirty-four (70.9%) of the 189 qualifying females completed the study as did 389 (73.0%) of the 533 qualifying males. Of those who discontinued, 23 (12.2%) of females withdrew because of an adverse event compared with 45 (8.4%) of males.

Reasons for exclusion:
The largest percentage of subject were excluded due to familial heart disease 870 (37.5%) and not following a low fat diet 670 (28.9%). A history of heart disease 445 (19.2%) and prohibited medications (including cyclosporine, itraconazole, ketoconazole, other systemic azole antifungal medications), erythromycin, clarithromycin, nefazodone, niacin > 500 mg/day, any medicine to lower cholesterol, and oral corticosteroids) 395 (17.0%) were the next most common reasons for exclusion. Heavy alcohol use, a history of liver disease or hepatitis, and poor/fair health status each accounted for between 9-10% of reasons subjects were excluded from the study.

*Comment: **Table 076-7** below shows participant responses to the self-administered medical history form of the 981 who answered "Yes" to "obtain this product and use it" (question 2 of the self-selection form). None of these people actually took the product.*

Table 076-7. Self-Administered Medical History Form Responses

Question	***# Responding, "Yes"***
Ever had hepatitis or liver disease?	*32*
Taking cyclosporine currently or within 4 weeks?	*0*
Taking itraconazole currently or within 4 weeks	*1*
Taking ketoconazole or similar currently or within 4 weeks	*0*
Taking erythromycin currently or within 4 weeks	*1*
Taking clarithromycin currently or within 4 weeks	*0*
Taking nefazodone currently or within 4 weeks	*0*
Taking > 500 mg niacin/day or within the past 4 weeks	*18*
Taking drugs to lower cholesterol currently or within 4 weeks	*40*
Taking Posicor currently or within 4 weeks	*0*
Taking oral corticosteroids currently or within 4 weeks	*4*
Alcohol consumption: 3 drinks per day *> 3 drinks per day*	*30* *18*

One hundred forty-four (14.7%) of subjects who stated they would buy and use the product were not qualified to do so in the above risk categories. None of them were treated. This data reveals a potential safety risk in the OTC market, where subjects self-select using this study label.

A larger percentage of females 228 (22.4%) were excluded from the study because of young age than males 123 (9.5%) and a larger percentage of males 191 (14.7%) were excluded for heavy alcohol use compared with females 23 (2.3%). Two hundred ninety-eight (22.9%) males were excluded because of heart disease compared with 147 (4.4%) females.

Comment: The age requirements for this study differed for males and females.

There were 720 subjects with a baseline LDL measurement, 568 with an LDL measurement within the day range for Visit 2, and 494 with an LDL cholesterol within the day range of Visit 4. The total number of subjects with an LDL value counted as a Visit 4 value was 527.

Thirty percent of subjects called their personal doctors about eligibility for the drug.

Efficacy:
Primary Endpoints
There were 568 subjects (of 722) with both a baseline and Visit 2 LDL cholesterol measurement, with a mean reduction of 21.7%. There were 493 subjects at Visit 3 and

494 subjects at Visit 4 who had LDL cholesterol measurements. The mean percent reduction at Visit 3 was 20.7%, and at visit 4 the mean percent reduction was 23.9%.

Table 076-8. All Qualifiers on Lovastatin 10 mg – Mean Change (%) from Baseline: LDL Cholesterol (mg/dl)

Visit	N	Baseline Mean	Treatment Mean	Mean
2	568	148.7	116.1	-21.7
3	493	149.0	117.9	-20.7
4	494	149.1	113.3	-23.9

Secondary Endpoints

The mean percent reductions in total cholesterol relative to baseline were similar at Visits 2 and 3, 12.9% and 13.1% respectively, and slightly greater at Visit 4, 15.7%. The mean percent change in HDL was an increase of 6.9%, 7.4%, and 6.0% at Visits 2, 3 and 4 respectively. Subjects with a baseline HDL < 35 mg/dl had a greater mean percent increase in HDL (17.3, 20.7, and 18.8 at Visits 2, 3, and 4 respectively) than those whose baseline HDL was ≥ 35 mg/dl (3.0, 2.4, and 1.5 at Visits 2, 3, and 4 respectively). The mean percent change in the ratio of total cholesterol to HDL was reduced at each of the study visits. There was no clear evidence of consistent changes in triglycerides over the course of the study. Approximately 90% of subjects had a decrease in LDL cholesterol after 8 weeks of therapy and the decrease was still seen at six months.

Comment:
Meaningful efficacy conclusions cannot be drawn from the data in Protocol 076 for the reasons previously stated (see page 15). Whether lowering total and LDL cholesterol and raising HDL in this study population results in clinical benefit (i.e., reduced incidence of heart attacks, angina or strokes) is unknown.

Subjects received information on following a healthy diet when they entered the study. The sponsor did not collect information about who modified their diets while participating in the study (unlike in efficacy trial 075). Improvement in cholesterol could have been secondary to dietary change and may not solely reflect drug effect.

Males tended to have both higher (approximately 7 – 8 mg/dl) baseline and post-treatment LDL cholesterol (approximately 5.5 – 7.5 mg/dl) values than females; however, the percent changes were similar for both genders. Males had slightly lower baseline and post-treatment total cholesterol values although the mean percent changes were similar for males and females. Males had lower HDL values then females at baseline and tended to have slightly larger post-treatment percent increases. Males had a higher ratio of total cholesterol to HDL than females, but the mean percent change values did not exceed 2.2%. There were no apparent gender differences for triglycerides.

Persistence
The number of subjects taking any medication since the previous visit were 630 (87.3%) at Visit 2, 537 (74.4%) at Visit 3 and 504 (69.8%) at Visit 4. The rate of decline in persistence appeared consistent over the first 2 visits and then flattened by the last visit. The sponsor states that the loss of subjects at each visit is not necessarily cumulative in their calculations. A subject could have fallen outside the day range for a particular visit and therefore excluded from the interval, but was then included in a subsequent interval.

Compliance
Of those who were on drug at Visit 2, Visit 3 and Visit 4, the number taking at least 75% of their medication (compliance ≥ 75%) was 542/630 (86.0%) at Visit 2, 466/537 (86.8%) at Visit 3, and 441/504 (87.5%) at Visit 4.

Four hundred eighty-six (76.1%) of 639 subjects who took 1 or more tablet took at least 75% of their medication across the study. The sponsor states that this compliance rate is somewhat lower than for the interval compliance rates (i.e., Visits 1-2, 2-3, 3-4) because the number included subjects who were either lost to follow-up or did not return their packaging, but had been documented at having taken study medication at some time during the trial. **Table 076-9** summarizes the relationship between compliance and efficacy.

Table 076-9. Relationship of Compliance and Efficacy at Visits 2 and 4.

% Compliance Visit 2	N	Mean % LDL Change
0 – 24	3	-4.97
25 – 49	3	-35.27
50 – 74	20	-15.01
75 – 100	530	-22.01
% Compliance Visit 4		
0 – 24	4	-9.43
25 – 49	6	-22.29
50 – 74	56	-13.11
75 – 100	423	-25.67

Comment: Those in the 75-100% compliance group for both visits had a larger LDL reduction than those subjects in the 50-74% group. The number of subjects in the other groups was very small and could not support any conclusions.

The sponsor states that the only predictor significantly associated with the probability of being persistent was the baseline total cholesterol $p = 0.009$. The higher the total cholesterol at baseline, the greater likelihood the subject was to be persistent.

Comment: The sponsor looked at age, gender, and level of education and considered both total and LDL cholesterol for its logistic regression model. The sponsor did not evaluate what if any relationship interaction with a personal physician had with

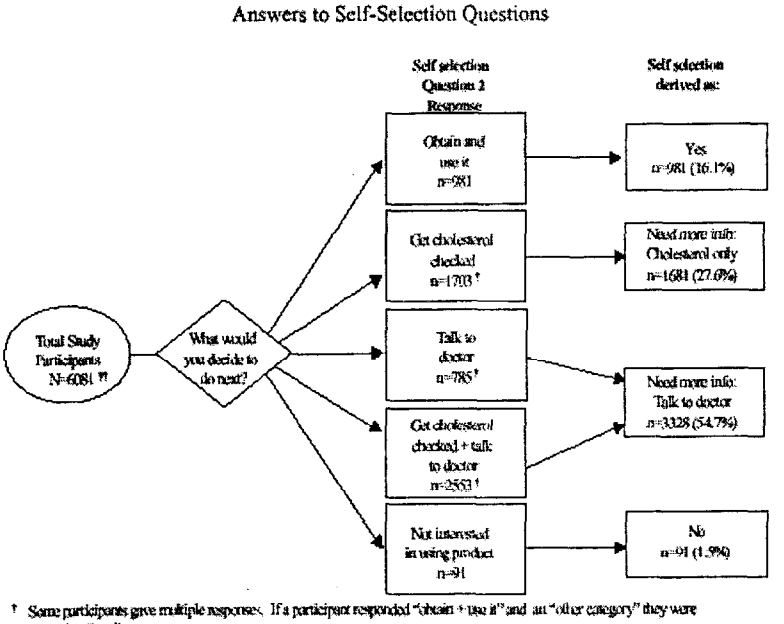
persistence. It would be of interest to know in an OTC setting, if subjects persisted because of encouragement from their physician, or if persistence was independent of this factor.

The sponsor did not find a correlation between demographics, baseline cholesterol and compliance. The sponsor hypothesizes that this is probably due to the fact that most subjects who were persistent were fairly compliant.

Comment: A subject could not be compliant in this study without being persistent.

Self-Selection
A total of 6081 (99.8%) participants completed the self-selection process. Fourteen responded to the advertising and visited the pharmacy but did not provide self-selection data and were not included in this analysis. **Figure 076-2** depicts how the self-selection was derived from subjects' responses to the 2 self-selection decision questions.

.Figure 076-2. Self-Selection Responses (Sponsor's Figure 6)



† Some participants gave multiple responses. If a participant responded "obtain + use it" and an "other category" they were counted as "yes."
†† 14 participants were missing self selection data
Note: 2662 study participants (981 + 1681) were likely to buy lovastatin.

The sponsor stated that self-selection question number 2 approximated the participant's true purchase behavior, and the subsequent self-selection study was designed so the participant actually made the decision whether to purchase.

Most (5009/6081 or 82.4%) participants, (**Figure 076-2**) needed more information before they could decide what to do. Nine hundred eighty-one (16.1%) said they would obtain and use the drug. Only 91 (1.5%) subjects said they were not interested in using the product.

The sponsor states that for the self-selection analysis, a participant's eligibility for lovastatin was determined from the responses on the medical history questionnaire, and did not include the actual results of the lipid test at the study site.

The sponsor states that eligibility per label was examined with and without the following set of exclusions: required low-fat diet, family history of heart disease, excessive alcohol use, poor health status, and use of ketoconazole. With the exception of ketoconazole, which the sponsor states was not included on the proposed label at the time of printing, these were considered exclusions in the protocol but were not subsequently retained as exclusions to nonprescription lovastatin.

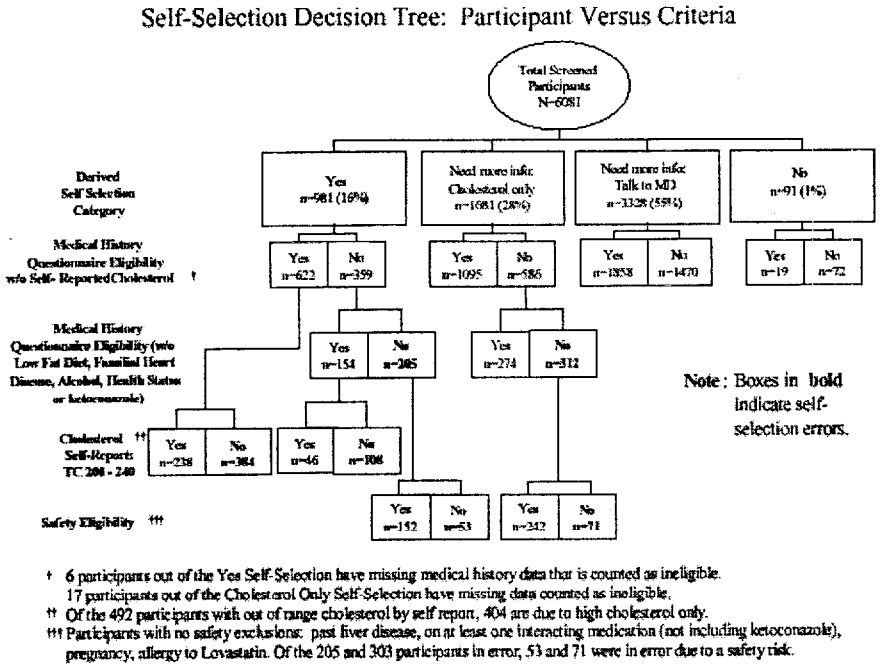
Comment: If subjects are considering self-medication for cholesterol, then conditions or risk factors that might make self-selection inappropriate (family history of heart disease, alcoholism, use of certain medications, etc.) should be warnings on a label.

Subjects were in "error" if they:
1. were ineligible for lovastatin and self-selected to obtain and use it
2. self-selected "Need more information: Cholesterol Only" and were ineligible for lovastatin for reasons other than cholesterol.

Comment: Subjects could only be in error if they were likely to buy lovastatin.

Figure 076-3 depicts the self-selection results as a flow diagram beginning with the participant's self-selection decision and detailing the eligibility along with the errors. The boxes with **bold** text represent the participants with self-selection errors.

Figure 076-3. Self-Selection Decisions (Sponsor's Figure 8)



† 6 participants out of the Yes Self-Selection have missing medical history data that is counted as ineligible.
17 participants out of the Cholesterol Only Self-Selection have missing data counted as ineligible.
†† Of the 492 participants with out of range cholesterol by self report, 404 are due to high cholesterol only.
††† Participants with no safety exclusions: past liver disease, on at least one interacting medication (not including ketoconazole), pregnancy, allergy to Lovastatin. Of the 205 and 303 participants in error, 53 and 71 were in error due to a safety risk.

When including requirements of a low-fat diet, history of family heart disease, excessive alcohol use, poor health status, and ketoconazole, 1329 (21.9%) subjects were not eligible. Without the exclusions listed above, 1009 (16.6%) of all study participants were not eligible according to the label. This group represented 37.9% of those who were likely to buy lovastatin. There were 404 participants (40% of 1009 ineligibles) who were likely to buy lovastatin but who reported their total cholesterol as >240 mg/dl. These 404 were otherwise eligible based on the label.

One hundred twenty-four (4.7%) of the 2662 who were likely to buy lovastatin were in the "safety risk" group. This group was defined as study participants with the following:

1. history of liver disease (72 subjects)
2. taking at least 1 interacting medication as per the study label (not including ketoconazole) (44 subjects)
3. able to become pregnant (3 subjects)
4. allergy to lovastatin (8 subjects)

There were 44 of the 2662 (1.6%) who took a contraindicated medication.

Comment:
Since ketoconazole, mibefradil dihydrochloride, protease inhibitors and coumarin were not listed on the study label, there may have actually been more than 44. The study protocol did not provide a way to confirm that the subjects were accurate in their reporting of interacting medications. It might have been useful to require subjects to

bring a list from their physician of medications they were taking. Therefore, it is not clear that subjects self-selected properly for the contraindicated medications category.

Three subjects were considered to have a pregnancy risk. The label warned pregnant and nursing women not to use the product, and the indication was for women 55 years of age or older. If this product is approved for OTC use, the pregnancy warnings should be further strengthened.

Other self-selections errors were 165 (6.2%) subjects with high cardiovascular risk, 163 (6.1%) who were younger than the required age for the study, 73 (2.7%) who were on other cholesterol-lowering drugs, and 88 (3.3%) with cholesterol <299 mg/dl, unknown cholesterol, or "problem/borderline high." Fourteen subjects in the error group were taking oral corticosteroids.

No differences were observed in self-selection based on either a higher education level or a lower education level compared to the overall study population. A larger proportion of the "at least some college" educated consumers (57%) compared with those with no college (51%) "needed more information: talk to MD."

Of the 6061 participants with both a medical history and a pharmacist eligibility decision, there were 225 (3.7%) instances, when the pharmacist considered a participant to be eligible, but the participant was actually ineligible by label criteria. In the subset of 981 subjects who indicated they would obtain and use lovastatin, there were 25 (2.5%) cases where the pharmacist would have been in error (per label) or would have erroneously permitted the participants to get the drug.

Comment: As the study progressed, the sponsor notes that certain conditions of exclusion were unclear to the pharmacists and clarification was provided. Among these were "fair health," what to do if a participant did not know his medications, low-fat diet, use of age in the pregnancy risk assessment, reporting age too young, missing allergy information, missing information about alcoholism. A computer algorithm excluded some subjects that pharmacists did not.

A comparison of the self-reported total cholesterol with the actual cholesterol test revealed that of the 1351 subjects who reported a cholesterol between from 200 – 240 mg/dl, 636 (47%) were actually correct in their self-reporting. Among the 1416 who self-reported a cholesterol >240 mg/dl, 1147 (81%) were actually correct.

Comment: Most (715/1351 or 53%) subjects who thought they met the study criteria for cholesterol level, in fact, did not. Six hundred twenty-five (46%) of these subjects had cholesterol values > 240 mg/dl and 90 (7%) had cholesterol values <200 mg/dl. Thus, most subjects who thought they qualified on the basis of their total cholesterol values, did not, in fact, know their cholesterol.

There were no study questions that determined how well consumers understand the meaning of the components of the lipid profile.

Safety:
Seven hundred twenty-two subjects received lovastatin 10 mg and were evaluated for safety by the sponsor. Two hundred twenty-eight (31.6%) experienced at least 1 adverse event and 157 (21.7%) subjects experienced an adverse event that the sponsor thought was drug-related adverse. Seven subjects had serious adverse experiences that the investigator determined to be definitely not or probably not drug related. None of the 722 subjects was reported to have had clinically apparent liver disease during the 6-month trial.

Sixty (9.4%) subjects (who took the medication) discontinued due to a drug-related adverse experience. The sponsor noted that 4 subjects were not included in the count of patients discontinued due to an adverse experience. These 4 had an adverse experience that began during the primary study but completed the primary study and discontinued due to the adverse experience in the study treatment extension. The sponsor states that they will be counted as discontinued when the treatment extension data are summarized. The sponsor identified 4 subjects who discontinued the primary study due to a serious adverse experience unrelated to the study drug.

Comments:
In the efficacy trials (075, 016, and 061) the percent of subjects who discontinued secondary to drug-related adverse experiences was < 2%. In Protocol 075 there were 6/104 (5.8%) drug-related adverse experiences, none of which were thought to be serious. It is worrisome, but unclear why, the percentage of drug-related adverse event discontinuations was so much higher in this actual use trial.

Six hundred thirty-nine subjects actually took at least 1 tablet at some time during the study. Therefore, the 157 subjects who experienced an adverse event that was thought to be drug-related were actually 24.6% of the population who took the drug. This may not be the true number since not all of the adverse events were included in the database. Although 7 subjects experienced serious adverse events that did not appear to be causally related to the study medication, 3 subjects had hypertension and 2 of them had cardiac disease. One had diabetes and supraventricular tachycardia; one had angina pectoris prior to enrollment and underwent emergency angioplasty while enrolled; and the third was hospitalized while enrolled with chest pain, dyspnea, and elevated blood pressure. The third subject had an abnormal treadmill test, but a cardiac catheterization did not show coronary artery disease.

Comment: These subjects demonstrate that older people with serious medical conditions and who need the care of a physician will self-select to take OTC lovastatin.

Since no laboratory tests were performed, there is no safety information about the liver, or muscle (which are followed with laboratory tests when lovastatin is prescribed by physicians). Therefore, there may have been safety problems that were missed during this study.

Among the subjects who discontinued the study because of adverse events, 9 had HDL levels in the range of 58-81 mg/dl with a low Total Cholesterol/HDL ratio. Thus, subjects who may have had limited opportunity to derive clinical benefit put themselves at risk.

The most common types of adverse experiences thought to be related to study drug were flatulence 38 (5.9%), constipation 15 (2.3%), and headache 15 (2.3%). **Table 076-11** lists the side effects thought to be related to study drug.

The most frequently reported adverse experiences resulting in discontinuation were flatulence 9 (1.4%) and myalgia 8 (1.3%). The intensity of the myalgia adverse experiences was rated as moderate or severe for 6 of the 8 patients who discontinued. The outcome was reported as "recovered" for 5 of the 8. One subject had an elevated CPK. One subject experienced myalgia during the primary study, subsequently completed it, and discontinued due to myalgia in the study treatment extension.

Table 076-11. Side Effects Related to Lovastatin 10 mg. (Percents included ≥1%)

Side Effect	# (%)
Flatulence	38 (5.9)
Constipation	15 (2.3)
Headache	15 (2.3)
Myalgia	13 (2.0)
Diarrhea	12 (1.8)
Pain, abdominal	12 (1.8)
Acid regurgitation	8 (1.3)
Dyspepsia	8 (1.3)
Rash	7 (1.1)
Asthenia/fatigue	6
Impotence	6
Pain, chest	6
Pruritus	6
Distention, abdominal	5
Dry mouth	5
Dermatitis	4
Insomnia	3
Mental acuity decreased	3
Paresthesia	3
Somnolence	3
Anorexia	2
Cramp, muscle	2
Dizziness	2
Gastritis	2
Libido decreased	2
Nausea	2
Pain, back	2
Weight gain	2
Akinesia/bradykinesia	1
Bowel sound abnormality	1
Depression	1
Dermatitis, allergic	1
Dream abnormality	1
Edema/swelling	1
Epistaxis	1
Fasciculation	1
Gastrointestinal disorder	1
Hypertension	1
Influenza	1
Memory impairment	1
Pain, anal/rectal	1
Pain, flank	1
Pain, leg	1
Pain, musculoskeletal	1
Palpitation	1
Pruritus ani	1
Rhinitis	1
Rosacea	1
Sleep disorder	1
Ulcer, gastric	1
Urinary urgency	1
Urticaria	1

Summary Comments:
The data from this actual use trial suggests that subjects who were compliant did reduce their cholesterol in this study, but this reduction is hard to interpret for reasons discussed in the comments in the review. The study does not consider HDL as a criterion for self-selection; thus many subjects with high HDLs used the product. The study does not provide evidence that consumers actually understand what constitutes a cholesterol risk. This trial demonstrated that most subjects who thought their cholesterol was within the 200-240 mg/dl range were not correct. Almost half of them in actuality had cholesterol > 240 mg/dl. Subjects with coronary artery disease and its risk factors self-selected to enter the trial.

The study label was not effective in guiding subjects to appropriately self-select based on their medical histories. The label did not list all contraindicated concomitant drugs, and thus was a poor one to test actual use. It is clear that many subjects did not understand what drugs or medical conditions preclude using lovastatin. The additional information they received about the drug through the informed consent process (which is unavailable in the OTC market place) biased the study. A better label would have urged volunteers to consult their private physicians if they: have cholesterol > 240 mg/dl; are confused about their cholesterol values; have a history of heart disease, diabetes, stroke, hypertension or liver disease; consume 3 or more alcohol containing beverages per week; or have questions about medications they are taking.

The trial did not demonstrate serious drug-related side effects during the 6 months on study drug, however one fourth of subjects on the study drug experienced related side effects. Since laboratory tests were not done, the safety information from this trial is incomplete.

Conclusion:
The sponsor proposed indication for this product in the OTC marketplace is medically unproven. This trial did not demonstrate that consumers can appropriately self-select to take lovastatin for the indication set forth. The trial demonstrated that compliance was low in the actual use setting compared with health care professional monitored settings. Information on adverse experiences was incomplete.

Protocol 077 – A Multicenter, Open-Label Study to Evaluate Compliance and Persistence in Patients Who Self-Select to Receive Lovastatin 10 mg for Treatment of Moderate Primary Hypercholesterolemia (Total Cholesterol 200-240 mg/dl) in a Worksite Setting.

Purpose:
This study was designed to evaluate how consumers self-select when provided only with the proposed OTC market label and to evaluate consumer use of lovastatin 10 mg when provided with drug, proposed market labeling instructions, and periodic cholesterol checks in a setting where a nurse is available. The study sought to determine how many consumers would still be taking study drug at 6 months (persistence) and what percent of tablets they would be taking.

Objectives:

Primary

1. To evaluate the mean reduction in LDL cholesterol at the first follow-up visit and at 6 months

Secondary

1. To evaluate the ability of study participants to correctly self-select
2. To evaluate drug persistence and compliance over 6 months
3. To evaluate the effect of treatment on diet adherence
4. To evaluate tolerability

Investigators:

There were 10 nurse co-investigators at corporate worksites and 1 physician co-investigator reachable by a toll-free telephone number.

Inclusion Criteria:

1. Men 45 years or older and women 55 years or older without heart disease (i.e., heart attack or angina)
2. Total cholesterol measured on Day 1 was 200-240 mg/dl, and LDL was ≥ 130 mg/dl after a minimum 4-week trial of a low-fat diet to lower cholesterol immediately prior Day 1. Individuals who meet all other criteria, but have not been dieting (or who have been dieting for less than 4 weeks) would be directed to follow a low-fat diet for 4 weeks and then to return to the Health Center.
3. Subjects must be in good health without any debilitating disease.
4. Subjects must demonstrate a willingness to participate in the study as evidenced by written informed consent.
5. Subjects must be able to comprehend and comply with the study requirements.

Exclusion Criteria:

1. Participation in any drug study currently or within the past 2 months.
2. Any contraindication to the use of lovastatin, including allergy to prescription lovastatin, hepatitis, or history of liver disease.
3. Currently taking cyclosporine, itraconazole, ketoconazole (or other systemic azole antifungal medications), erythromycin, clarithromycin, nefazodone, or oral corticosteroids.
4. Taking any other cholesterol-lowering medication (including OTC niacin in doses > 500 mg/day) within the 4 weeks prior to the screening visit (Day 1).
5. Women of childbearing potential, pregnant women, or women who are breastfeeding.
6. History of heart or peripheral vascular disease.
7. History of heart attack before age 55 in parents or siblings.
8. Consumption of ≥ 3 alcohol-containing drinks per day on most days of the week.

Comment: Not all drugs that are contraindicated with lovastatin were part of the exclusion criteria.

Study Design:
Study sites were multiple worksite Health Centers in the United States. Each center was equipped with a CHOLESTECH® desktop cholesterol analyzer and an on site nurse-investigator would take all measurements and collect and record all study data. At a worksite health fair interested employees and spouses could have their cholesterol tested and obtain information on a low fat diet and exercise. Those who expressed an interest in study participation were invited to come to the Health Center after at least 4-weeks on the low-fat diet (Study Visit 1). Anyone unable to attend the health fair was permitted to receive a cholesterol check and diet information in the company's Health Center from the nurse-investigator.

Comment: The sponsor provided common advertising copy for the fairs so as to ensure consistency in subject recruitment communications, even though the sponsor did not consider the Health Fair to be part of the study.

As part of the recruitment process, the ability of subjects to read and understand a label was not assessed.

At the first study visit, potential participants were given a product label to read, and a Self-Selection Decision, Self-Administered Medical History questionnaire and MEDFICTS (Meats, Eggs, Dairy, Fried foods, In baked goods, Convenience foods, Table fats, Snacks) dietary questionnaire to complete. The nurse reviewed the completed forms, recorded information on the case report form and assessed the participant's eligibility. This assessment was not communicated to the subject. The nurse allowed all individuals who self-selected and who reported following a low-fat diet to enroll. This was regardless of the nurse's opinion of the subject's eligibility. However, the nurse did exclude those with (safety risk) exclusion criteria #2, 3, and/or 5 above.

Comment: The MEDFICTS questionnaire develops a numeric score that takes into account what a subject eats and the quantity. It has shaded boxes that indicate foods that are high in fat, saturated fat, and/or cholesterol. In that regard, it teaches a subject what foods would be part of a low fat diet and which one would not.

Those who indicated their eligibility and signed the informed consent had a cholesterol analysis performed and were given lovastatin 10 mg (2 blister packs, 56 tablets total) packaged in cartons bearing the proposed market labeling. All subjects used the product according to their understanding of the indications, warnings and directions in the product label. Subjects also received a "Patient Information Card" at this and each subsequent visit. On the card was his/her current total and LDL cholesterol values, the days/times when testing was available in the Health Center, and a toll-free number to consult with the study physician, ask questions, or report adverse experiences.

Comment: The informed consent form reminded subjects that they should continue to follow the low fat diet throughout the study. Some subjects may have brought their cholesterol into study range with the diet.

The treatment indications the sponsor created did not follow NCEP guidelines for drug treatment of cholesterol. The informed consent section on "Prior Experience With Drug" is misleading. It tells the subject, "Research studies have also shown the MEVACOR® was effective in slowing the development of fat build-up (atherosclerosis) in middle-aged men with coronary heart disease." It does not mention that this has not yet been demonstrated for subjects who meet the entry conditions for this study and take lovastatin 10 mg.

The informed consent form also emphasized the label exclusions, so subjects had more exposure to the reasons they should not use the product than would the typical OTC consumer. Thus, the informed consent process could bias the self-selection process.

Subjects were not specifically directed to call the study physician at the toll-free number before taking the first dose of study drug; however, the nurse instructed them to read the package label and accompanying materials carefully before use, and would note the toll-free number for the study physician. The sponsor states that this approach was intended to ensure that contact with the study physician was patient-initiated and self-motivated. When contacted, the study physician reviewed the subject's medical history and determine his/her eligibility based on all inclusion/exclusion criteria. If the physician determined a subject to be ineligible, he instructed the subject was to discontinue the study and return all study drug to the nurse.

Comment: If contact with the study physician was to be completely self-motivated, the telephone number should not have been specifically pointed out by the nurse. Also, the informed consent form used bold print to remind subjects that they could call a study doctor. These incentives to contact a doctor are not available in the OTC setting and in this regard, the study does not mimic actual use.

The label on the study carton panel did not mention all of the drugs that are contraindicated with lovastatin, and thus was poorly designed to evaluate the ability of subjects to properly self-select.

Subjects with a total cholesterol from 190-199 or 241-250 mg/dl or an LDL from 120-129 could have one cholesterol recheck within 2 weeks that could be used to determine study eligibility. Subject enrollment was to continue until 660 subjects were determined to be eligible by the study doctor.

If, at Visit 1, subjects had questions or concerns about whether they should take lovastatin, they were allowed to go home without study medication and call the study physician. If the physician determined a subject was eligible, he/she could return to the Health Center to sign the informed consent, have cholesterol measurements taken and receive study medication.

Subjects were instructed to report any adverse events either to the nurse at the next visit, or to a study nurse of physician via a toll-free telephone number. They had to return to

the study site on their own initiative to obtain a new supply of 56 tablets of lovastatin at approximately week 8 (Visit 2) and week 16 (Visit 3). All subjects were directed to return for the final study visit (Visit 4) 8 weeks after Visit 3 or 24 weeks after Visit 1, whichever is the shorter interval. At each visit, used blister packs, cartons and remaining study drug were collected and an accounting was done.

At each study visit a lipid profile was measured and a MEDFICTS Dietary Assessment Questionnaire was completed. Subjects were encouraged to make their visit at least 2 hours after a meal. The time since the last meal (<2 or ≥2 hours) was recorded. Subjects for whom the LDL cholesterol value had not gone down by the Week 8 measurement, were advised to have a cholesterol retest within a few days. In the interim the subject received a new 8-week drug supply until a decision was made about continuing the study. If the additional measurement did not show a reduction in LDL cholesterol, the subject could consult with the study physician regarding the appropriateness of continuing study drug. **Table 077-1** depicts the events that occurred at each study visit.

Comment: A "2-hour fast" is not a fast.

Subjects were instructed via the product label to take 1 tablet of study drug daily with the evening meal. If during the study period a course of erythromycin was prescribed for a study subject, he/she was instructed to temporarily interrupt lovastatin therapy until the antibiotic regimen was completed.

Table 077-1. Occurrences at Each Study Visit

Occurrence	Visit 1	Visit 2	Visit 3	Visit 4
Subject reads study label and completes self-selection form	X			
Subject completes self-administered medical history form	X			
Nurse reviews responses on history form and records assessment regarding appropriateness for study	X			
Informed Consent obtained	X			
Lipid profile measured (Total, LDL, HDL, Triglycerides)	X	X	X	X
Subject receives study drug and Patient Information Card	X	X	X	
MEDFICTS Dietary Assessment Questionnaire complete by subject	X	X	X	X

The sponsor planned that LDL cholesterol at approximately 8 weeks would be used to address the main primary hypothesis for efficacy. The LDL measurement at 24 weeks would be assessed in subjects who were still on the medication to show sustained effect. Persistence would be assessed by determining the number (%) of subjects who are still on

medication at 6 months. Compliance would be determined as in Protocol 076. The relationship between compliance and percent LDL reduction would be determined. Accuracy of self-selection and compliance with label instructions to call the study physician would be characterized. Adherence to diet while on treatment would be determined by baseline and follow-up MEDFICTS scores.

Comment: There was no placebo comparison to study drug. That plus the variability of cholesterol with diet and absence of repeated baseline blood drawings confounds efficacy data.

Any adverse experience information received on the toll-free line from a subject would be recorded on a case report form and submitted to Premier (data management contract research organization). Serious adverse experience information would be reported to Merck within 24 hours. Adverse experiences were evaluated with regard to intensity (mild, moderate, severe), seriousness, action taken, relationship to test drug.

Results:

The sponsor states that the study was terminated early due to poor enrollment and program timeline constraints, and that expanded subject recruitment efforts were unsuccessful. The sponsor offers the following reasons for low enrollment:

1. Nurses reported that they thought the mandatory diet delayed study entry and discouraged participation
2. Word-of-mouth communication in the work site population
3. Nurses were inexperienced in conduction clinical trials and the study-related activities were additional and secondary to their normal daily occupational health work
4. A number of the health centers were inconveniently located for employees to access during the workday (during their limited break time)

Since no subject reached the primary time point of interest (6 months), the sponsor states no data analyses were performed.

Of the 660 subjects that the sponsor planned to enroll in the study, 128 were screened and 86 entered. Of these, 71 were male (ages 37-71) and 15 were women (ages 48-74). The sponsor states that although many of the participating work sites were "blue collar" businesses, the majority of enrolled subjects were "white collar" workers, based on the level of education that most study subjects reached.

Comment: Both men and women younger than the minimum age for the study were enrolled. Sixty-six subjects had a minimum of some college education. Thirty-four enrolled subjects had total cholesterol values > 240 mg/dl and 3 had total cholesterol values < 200 mg/dl. This is reflected in the mean total cholesterol value for the enrollees, which was 239.8 mg/dl. Fifteen subjects had LDL cholesterol values < 130 mg/dl. Thus, more than half of subjects enrolled in this trial did not meet inclusion criteria based on their cholesterol values.

Forty subjects had lipid values performed at Visit 2 and 5 subjects at Visit 3.

Comment: Fourteen of the 40 subjects who had cholesterol values performed at Visit 2 and 3 of the 5 who had cholesterol values obtained at Visit 3 had lipid values that qualified them for enrollment in the trial. One enrolled subject had a total cholesterol of 234 but LDL could not be determined because of a triglyceride level of 641.

No subjects completed the 24-week trial. Eleven subjects completed 12 weeks or more of the study prior to its termination. The reasons that all 86 enrolled subjects discontinued are presented in **Table 077-2.**

Table 077-2. Reasons 86 Subjects Discontinued Participation in the Study

Reason for Discontinuing	Number (%)
Adverse Event	1 (1)
Lost to follow-up	14 (16)
Ineligible per toll-free physician assessment	19 (22)
Early study termination	52 (60)

Four subjects described clinical adverse events. None were considered to be serious. In three subjects these were considered to be possibly drug related:

1. One subject had worsening of erectile dysfunction on day 1 of the study;
2. One subject experienced "heart racing" on day 18;
3. One subject experienced "chest tightness" on day 5. This subject interrupted his study medication.

The subject who discontinued the study had decreased visual acuity on day 1 of the study. This was thought by the investigator to probably not be lovastatin related.

There were no safety laboratory analyses done during this trial.

Summary: The trial was terminated early and there is not enough data available to make any specific recommendations.

Conclusion: Protocol 077 does not provide enough data to support the case for allowing lovastatin 10 mg to go OTC.

Protocol 079 – A Multicenter, Open-Label, Storefront Study to Evaluate Compliance and Persistence of Lovastatin 10 mg in Patients Who Are Qualified by a Telephone Label Reinforcement Service for Treatment of Moderate Primary Hypercholesterolemia (Total Cholesterol ≤240 mg/dl, LDL ≥130 mg/dl).

Purpose:

The purpose of this study was to obtain additional information on the efficacy and safety of lovastatin and the persistence of use in subjects who are dispensed lovastatin 10 mg in the over-the-counter setting. The sponsor states that recognizing the challenges of interpreting detailed label instructions, a telephone label reinforcement service was employed to triage participants who may be eligible for lovastatin 10 mg.

Objectives:
The primary objective of the study was to evaluate the mean reduction in LDL cholesterol at the 8-week follow-up visit.

There were 2 secondary objectives:
1. To evaluate the ability of subjects to remain on lovastatin 10-mg treatment over the 8-week study period.
2. To evaluate the tolerability of lovastatin 10-mg as measured by the incidence of clinical adverse experiences.

There was an "exploratory objective" to characterize the proportion of subjects who go through each stage of the telephone label reinforcement service.

Comment: This study did not attempt to evaluate appropriate self-selection.

Investigators:
There were 7 centers with a nurse co-investigator at each center and a toll-free number physician consultation center in the United States participated in the study. The physician investigator in this study was the same one for Protocol 076. Of the 7 centers 2 were in Texas, 2 were in Florida, and 3 were in Illinois. All nurses in the study were registered nurses, and some had training beyond that.

Inclusion Criteria for Telephone Qualification:
1. Men 40 years or older; women 55 years or older.

Exclusion Criteria for Telephone Qualification:
1. Participation in any drug study within 2 months prior to this study's start or during this study.
2. Any contraindication to the use of lovastatin, including allergy to prescription Mevacor™, diagnosis of hepatitis, or a past history of liver disease.
3. Currently taking mibefradil dihydrochloride, cyclosporine, itraconazole, ketoconazole (other systemic azole antifungal medications), erythromycin, clarithromycin, nefazodone.
4. Ever taken any other prescription cholesterol-lowering or triglyceride-lowering medication.
5. Taking any over-the-counter cholesterol-lowering medication (including niacin in doses >500 mg/day, or Cholestin™, of oral corticosteroids within 4 weeks prior to the screening visit (telephone interview).
6. Women of childbearing potential, pregnant women, or women who are breast-feeding.
7. History of heart disease, angina, stroke, transient ischemic attacks, or peripheral vascular disease. Any invasive procedure (PTCA, CABG).
8. Consumption of 3 or more alcohol-containing drinks per day on 4 or more days in a week.
9. Taking more than 1 prescription antihypertensive agent.

10. History of diabetes.
11. Subjects who know their total cholesterol was <190 mg/dl or >250 mg/dl.

Comment: The criteria for subject selection were more extensive in this study than in Protocol 076 or 077. The sponsor notes that during preliminary screening, the telephone service asked participants if they could read or understand English without assistance; if not, subjects were excluded. Since there was no formal literacy test administered, it is not clear how well subjects actually read and understood English. Subjects with any association with a company that manufactures pharmaceutical, medical, or healthcare products were excluded.

A family history of coronary artery disease, especially prior to the age of 55 is a risk factor for myocardial infarction. Those subjects having a positive family history of coronary artery disease, should have been excluded and urged to see their personal physicians.

The exclusion criteria did not include protease inhibitors or coumarin anticoagulants. Hormone replacement therapy was not mentioned.

There were inclusion and exclusion criteria at the study site, also.

Inclusion Criteria at Site:
1. Subjects must have demonstrated a willingness to participate in the study as evidence by written informed consent.
2. Total cholesterol measured on Day 1 must have been ≤ 240 mg/dl and LDL cholesterol must have been ≥ 130 mg/dl.
3. Subjects must have been able to comprehend and comply with study requirements.

Exclusion Criteria at Site:
1. Subjects who were not currently taking anti-hypertensive medication were excluded if they had a sitting diastolic blood pressure ≥100 mm Hg. Subjects with a sitting systolic blood pressure ≥180 mm Hg and a diastolic pressure ≤90 mm Hg (isolated systolic hypertension) were excluded.

Comment:
Diastolic hypertension is associated with increased risk of cardiovascular events. Men with isolated systolic hypertension (systolic > 158 mm Hg, diastolic < 82 mm Hg) have a cardiovascular mortality rate 2.5 times higher than individuals with normal diastolic pressures and systolic pressures < 130 mm Hg).[1] If the sponsor does not think subjects with hypertension should be using an OTC cholesterol-lowering product, then it should demonstrate that subjects know that they have hypertension (usually a silent disease), and can appropriately self-select.

Study Design:
This was an open-label, uncontrolled, multicenter study designed to screen by telephone a sufficient number of participants to enroll 400 subjects on therapy with lovastatin 10 mg

per day. The duration of the study was approximately 8 weeks. Participation in an extension study was offered at the end of the trial.

Advertising, aimed at diverse socioeconomic and racial, middle aged and older audiences, was placed in the media (television, radio, newspaper) and directed interested consumers concerned about their cholesterol to call a toll-free telephone label reinforcement service. The advertisements indicated that callers should know their total cholesterol, not have heart disease or diabetes, and should not be taking prescription medications to lower cholesterol. The sponsor states that to ensure consistency in patient recruitment communications, the IRB approved common advertising copy.

Individuals who called were assigned a unique patient identification number. Participants were questioned by a telephone screening script, which represented the telephone inclusion/exclusion criteria. Subjects who did not know their total cholesterol value and were not excluded by any other telephone criteria, were allowed to proceed to the storefront study site for a cholesterol test; participants who knew that their total cholesterol value was < 190 mg/dl or > 250 were excluded from the study. Participants were required to call their doctor or pharmacist if they could not determine if they were taking one of the prohibited medications. Participants, deemed potentially eligible and who were interested in entering the study, were scheduled for a storefront study visit and instructed that to obtain an accurate cholesterol reading, they should not eat any food within 6 hours of their visit.

Comment: The telephone interviewer read a list of 11 different lipid lowering drugs; (generic and trade names). Subjects were also asked specifically if they used: Cholestin, prednisone, Medrol, methylprednisone, Decadron, dexamethasone, Hydrocortone, or hydrocortisone, erythromycin, clarithromycin, Ery-Tab, PCE, Eryc, Ilotycin, Ilosone, E.E.S., Ery ped, Eryzole, Erythromycin, E-mycin, E-Base, Eramycin, Wyamycin-S, or Biaxin. Subjects also had to respond to whether they were taking: "mibefradil which is known as Posicor," " nefazadone which is known as Serzone," "cyclosporine which is known as Neoral or Sandimmune," "ketoconazole which is known as Nizoral, or itraconazole which is known as Sporanox."

The inclusion and exclusion criteria in this trial were more specific than the study label warnings with regard to past history of coronary artery disease, hypertension, and stroke. This study was not assessing the ability of a subject to appropriately self-select. However, safety information derived from this trial, because of the exclusion criteria, may not be representative of what would be seen in the actual OTC setting.

The sponsor states that the study label, otherwise known as the "Restricted Access Label," was designed to reinforce appropriate consumer behavior after the drug was dispensed. It was not in "Drug Facts Format." This label differed from that of Protocols 076 and 077 in that it had a specific section boxed off and entitled "Drug Interaction Warning." In this section drugs were listed in both generic and proprietary names. The warnings section "Do not use Mevacor CC if you" listed heart attack, angina, stroke, diabetes, high blood pressure. Heart attack and angina had been part of the "Talk to the

Study Doctor Before Using" section in the "Pharmacy" label. The exclusion criteria, label, and informed consent, as in the other studies did not mention warfarin anticoagulants.

The Restricted Access Label did not mention oral corticosteroids. The sponsor states that this category of product was added to the clinical study restrictions because of the potential for such medication to raise serum cholesterol levels.

Subjects were not asked if their cholesterol was 200-240 mg/dl, the target treatment group for the proposed OTC use of lovastatin. Instead, they were asked if they thought it was 190-250 mg/dl. This might have mislead consumers about who could use the product.

The telephone interviewer gathered information about smoking habits and about family history of heart disease (father or brother before age 55, mother or sister before age 65) but these were not inclusion or exclusion criteria. If subjects stated that they did not try to follow a healthy diet, the telephone interviewer sent diet information and told subjects to go on the diet and to report to the study site 4 weeks later for a cholesterol test to determine if they should enter the study.

The "fasting" requirement for this trial was expanded to 6 hours instead of 2 (as in Studies 076, 077). This may still be inadequate to achieve reliable test results.

Those participants who were considered potentially eligible based on their responses during the telephone interview were scheduled for a storefront study visit to determine if they qualified to receive lovastatin 10 mg. Those participants deemed ineligible were advised on the importance of cholesterol management and were mailed follow-up material. A brief follow-up telephone survey for market research purposes on the ineligible participants was conducted.

Visit 1 – Day 1
Potentially eligible subjects provided written informed consent, and if they had any questions, they could call the study physician.

Comment: The informed consent section, "Prior Experience with Drug," is misleading. It tells the subject, "Research studies have also shown the MEVACOR® was effective in slowing the development of fat build-up (atherosclerosis) in middle-aged men with coronary heart disease." It does not mention that this has not yet been demonstrated for subjects who meet the entry conditions for this study who take lovastatin 10 mg.

A fingerstick lipid profile, height, body weight and blood pressure were measured. Each participating storefront site was equipped with a CHOLESTECH L·D·X™ desktop fingerstick cholesterol analyzer and staffed by an investigator who was responsible for taking all measurements and collecting and recording all study data. Subjects who met entry criteria were given an 8-week supply (2 blister packs, total 56 tablets) of open-label lovastatin 10 mg (labeled as MEVACOR™ CC) and a Study Information Card. The

sponsor states that the study drug package had prototype nonprescription market label information on the front and back panels and, to encourage compliance, each blister back was imprinted with the days of the week, and week numbers 1-4. Subjects were instructed to return to the storefront after they had finished their medication (approximately 8 weeks).

Subjects whose values were marginal for total cholesterol (241 – 250 mg/dl) or LDL (120 – 129 mg/dl) were permitted to recycle back to the storefront to have their cholesterol rechecked for study eligibility. Subjects whose LDL cholesterol could not be calculated by the CHOLESTECH™ analyzer using the Friedewald Approximation (See page 14) because of triglycerides ≥ 400 mg/dl, were also permitted to recycle back for retest. For each case of an uncalculated LDL value, the site investigator had to consult with the study physician to determine if re-testing could be permitted. If so, the subject was advised to fast for 12 hours before their retest. The maximum number of re-tests permitted were 2, one for each reason.

Comment: The lipid test criteria, for participation in this protocol, were loose.

The sponsor used different fasting criteria for the test and the retest. Thus, subjects were enrolled in the study who, had they fasted 12 hours initially, may not have qualified. Re-testing enabled the sponsor to qualify subjects who may not have met criteria with 1 value but did meet criteria with another one. Values were not averaged; the best of the 2 values was the one that was counted.

Subjects were required to sit for 5 minutes and have 3 blood pressure measurements, each separated by 1 minute. The average of the 3 readings was used to determine eligibility. Those subjects with an average sitting diastolic pressure ≥ 90 mm Hg and <100 mm Hg were eligible to enter the study, but were advised to talk to a private physician if they had been previously undiagnosed or if they were taking 1 antihypertensive medication. Those subjects with an average sitting diastolic blood pressure of ≥100 mm Hg were not eligible to receive study medication.

Subjects who received study drug were instructed to take it according to the label (1 tablet with food every evening). Each carton of study drug contained a patient package insert, reminder stickers, and an informational brochure. The Study Physician Co-Investigator was available at a toll-free number for patient-initiated and site-initiated telephone consultations, to answer any study-related questions, and to receive reports of adverse experiences. A nurse was also available at that number. If during the study period erythromycin was prescribed for a subject, the informed consent form directed the subject to call the study physician, who instructed the subject to temporarily interrupt lovastatin 10-mg therapy until the antibiotic regimen was completed.

All enrolled subjects received information describing a cholesterol-lowering diet and a healthy lifestyle, including exercise. They were told to limit alcohol to no more than 2 drinks per day during the study treatment period. The site investigator instructed subjects to call the study site for an appointment before they finished the study medication.

Follow-Up Visit (Week 8)
After a subject completed Visit 1 there were no further reminders to return for the follow-up visit. At the follow-up visit (approximately week 8), subjects returned any unused drug, empty blister packs and cartons, and had a lipid profile performed. The site investigator accounted for drug use (by comparing the tablets used to the total days since the first visit) and collected clinical adverse experience information. If after 16 weeks a subject had not returned, the site investigator attempted to contact the subject and persuade him/her to return for the follow-up visit.

Comment: The site investigator asked a "non-leading question about health status since last visit." Without specifically asking subjects about adverse experiences on the drug, the sponsor may not have obtained complete information about symptoms that subjects experienced.

A treatment extension to the protocol was offered to allow subjects to continue on drug therapy. The sponsor states that results from this treatment extension will be summarized in a separate Clinical Study Report.

Table 079-1 depicts the schedule of clinical observations, laboratory measurements and procedures for the study.

Table 079-1. Schedule of Clinical Observations, Laboratory Measurements and Study Procedures.

Activity	**Telephone Interview**	**Storefront**	
		Visit 1	**Visit 2**
Subjects called Telephone Label Reinforcement Service	X		
Subjects signed Informed Consent		X	
Lipid Profile measured		X	X
Blood Pressure, Weight, Height measured		X	
Eligible subjects received Drug and Study Information Card		X	
Returned Drug Collected			X
Adverse Experience Information Collected			X
Addendum Consent to enter Extension Study			X

Evaluation Criteria
Efficacy – Cholesterol values were considered to be baseline from the Visit 1 cholesterol test (either the initial Visit 1 test, or the last re-test). LDL cholesterol at approximately 8 weeks was used to assess the primary efficacy variable. The other lipid measurements were summarized.

Comment: There was no placebo in this trial with which to compare lovastatin. Since subjects received information about diet and exercise in addition to the drug, a decline in the cholesterol values could be attributed to a combination of factors.

Persistence, Compliance – Persistence was summarized at Visit 2 by calculating the number (%) of subjects who returned for the visit having taken any tablets of study drug. At Visit 2, compliance was calculated in the subjects who were still taking drug by dividing the number of tablets taken by the number of days the subject had study drug.

Comment: As with Protocol 076, compliance is the clinically meaningful consideration.

Safety – An adverse experience was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a preexisting condition, temporally associated with any use of the study drug, whether or not considered related to the use of the product. Adverse experiences were recorded on the appropriate adverse experience case report form page and rated as to intensity:

1. Mild – Awareness of sign or symptom but easily tolerated
2. Moderate – Discomfort enough to cause interference with usual activity
3. Severe – Incapacitating, with inability to work or do usual activity.

The investigator recorded the action taken in response to the adverse event and assessed the relationship of the drug with the adverse event according the following ratings:

1. Definitely not (no relationship)
2. Probably not (relationship not likely)
3. Possibly (relationship may exist)
4. Probably (relationship likely)
5. Definitely (unquestionable relationship)

There were no laboratory safety measurements in this study.

Statistical Planning and Analysis:

The following groups of study participants were defined:

1. Telephone Screened Participants (All Study Participants): All who responded to the study advertising campaign and answered a questionnaire administered by the telephone label reinforcement service.
2. Nonqualifiers, Telephone Interview: Subset of screened participants who were not eligible for drug based on the telephone interview.
3. Potentially Eligible Subjects: Those eligible based on the telephone interview. They were offered an appointment at a storefront.
4. Lost Participants: Potentially eligible subjects who did not keep the storefront appointment.
5. Refused Participants: Potentially eligible subjects who refused to make a storefront visit appointment.
6. Nonqualifiers, Storefront: Potentially eligible subjects who went to the storefront but were disqualified from receiving study drug because of their cholesterol, blood pressure, unwillingness to sign the informed consent, inability to comply with study procedures, or

medical history information that should have been picked up during the telephone interview.
7. Qualifiers: Those potentially eligible subjects who met all criteria at the storefront appointment and were dispensed study drug.

The sponsor defined 95% confidence that the true mean LDL cholesterol reduction in this setting was within 80% of that seen in the reference population (14.7% [80% of 18.4% as seen in the reference population]) after 8 weeks of treatment.

Comment: The reference population is from the previously described efficacy trials. They were not assessed to demonstrate if a reduction of LDL impacts the risk of myocardial infarction, angina, or stroke.

Day ranges were applied to lipid measurements, but persistence and compliance were calculated for all patients who were dispensed study drug regardless of when the medication was returned to the storefront.

The percent change from baseline in LDL cholesterol at week 8 (Visit 2) was assessed using data from all study participants who had a baseline cholesterol measurement and were dispensed drug. The primary approach to this endpoint estimated missing values at Visit 2 and values falling outside of the Visit 2-day range by using the study participant's baseline LDL value. (The Visit 2-week [day] range was from 4 weeks [28 days] to 12 weeks [84 days]). The sponsor states that this approach is conservative since it assumes a missing value comes from a participant who did not achieve a reduction in LDL cholesterol from baseline. In a secondary approach, subjects with missing data points or points falling outside of the day range were not included in the Visit 2 analysis.

Persistence and safety were evaluated for all subjects who received study drug; compliance was evaluated for all subjects who were persistent.

Safety: The sponsor did not evaluate the safety data separately for subjects who actually took the study drug (were persistent).

Exploratory supplemental analyses were performed to determine the impact of demographic characteristics on compliance and persistence. The relationship between compliance and efficacy was explored by summarizing the percent change in LDL cholesterol by compliance level.

Assessment of the telephone label reinforcement service for selecting subjects for treatment was made by determining the proportions of subjects who proceeded through each stage of the service and enrolled in the study.

Comment: Subjects do not have a telephone label reinforcement service like this in an OTC setting.

Adverse experience data was summarized. Ninety-five percent confidence intervals were estimated for adverse events that occurred in ≥5% of subjects.

Results:
Patient Characteristics:
A total of 4878 people participated in the telephone screening process resulting in 1312 (26.9%) subjects who were potentially eligible and visited a storefront site.

Table 079-2 summarizes why subjects were excluded during the telephone screening process. Ten subjects (0.2%) participated in the telephone screening process twice and were assigned 2 different identification numbers. One repeat subject was detected at the second storefront visit and was disqualified. The remaining nine were not identified as duplicates during the conduct of the study. Thus the 4878 participants actually represent 4869 unique individuals but all calculations involving screened participants were based on 4878.

Table 079-2. Reasons for Exclusion During Telephone Screening Process.

Reason For Exclusion (Total Excluded 2559)	**Telephone Nonqualifiers N (%)**
Did Not Complete Call	145 (5.7)
Study Exclusion Criteria	199 (7.8)
Not Eligible Based on Product Label	2215 (86.6)
Self-Reported Cholesterol Not in Range	986 (38.5)
Prior or Current Lipid-Lowering Medication	727 (28.4)
Age Not in Range	320 (12.5)
Excessive Alcohol Use	256 (10.0)
History of Liver Disease	251 (9.8)
Use of Prohibited Medications	199 (7.7)
>1 Antihypertensive Medication	196 (7.7)
History of Heart Disease	117 (4.6)
Stroke	109 (4.3)
Diabetes	81 (3.2)

A total of 2319 (47.5%) subjects of the 4878 were potentially eligible based on the telephone screening. Four hundred fifty-three (19.5%) refused participation, 554 (23.9%) did not keep their storefront appointment, and 1312 (56.6%) scheduled and kept their appointment visit.

Of the 1312 subjects 460 (35.1%) received study drug. Eight hundred fifty-two potentially eligible subjects (64.9%) did not qualify to receive study drug. Seven hundred eighty-three (59.7%) did not qualify because of their cholesterol values; 13 (0.9%) did not qualify because of blood pressure values, and 56 (4.3%) did not qualify for other reasons. **(See Table 079-3.)**

Comment: Of the 4878 consumers interested in learning about the medication, only 460 (9.4%) actually qualified to take it. This low number is of concern regarding consumers' ability to properly self-select in the OTC setting.

Table 079-3. Summary of Qualified and Nonqualified Subjects

1312 Potentially Eligible Subjects	# (%) Subjects
Qualified	460 (35.1)
Nonqualified	852 (64.9)
Cholesterol	783 (59.7)
Blood Pressure	13 (0.9)
Other reasons	56 (4.3)

Comment: Among the nonqualified, 7 of the 852 (0.8%) were disqualified at the storefront but should have been disqualified by the telephone screening. Four subjects had liver disease, two were taking at least 2 antihypertensive drugs, and two were taking pravastatin.

Of the 4878 screened subjects, 58.0% were male, compared to 70.0% of the 1312 subjects potentially eligible subjects and 80.7% of the 460 qualified subjects. Thus, the proportion of subjects who were male, increased as the screening process progressed from the telephone to the storefront, and then to qualification for study drug.

Ages were similar for qualified and nonqualified subjects, having a mean age of approximately 58 years. Of the 1312 potentially eligible subjects, 1129 (86.1%) were Caucasian and 412 (89.6%) of the qualified subjects were Caucasian. Information about race was not collected during the telephone interview stage of the study.

All qualified potentially eligible subjects had a baseline lipid profile; 31 nonqualified ones did not (25 did not sign the informed consent, 5 were disqualified because of medical history, and a lipid profile could not be obtained on 1 subject). **Table 079-4** summarizes the baseline lipid values for all potentially eligible subjects who had their lipids tested (based on sponsor's Table 6).

Table 079-4. Baseline Lipids for All Potentially Eligible Subjects Who Had Cholesterol Test.

Lipid (mg/dl)		Qualified Subjects (N = 460)	Nonqualified Subjects (N = 821)
LDL cholesterol	Number	460	759
	Mean ± SD	147.2 ±11.8	150.5 ± 40.8
	Median	146	152
	Range	130-192	47-302
Total Cholesterol	Number	460	821
	Mean ± SD	223.3 ±11.7	241.2 ± 42.9
	Median	225	251
	Range	185-240	102-470
HDL Cholesterol	Number	460	805
	Mean ± SD	46.1 ± 13.2	52.6 ± 17.5
	Median	45	50
	Range	17-86	17-100
Total/HDL Cholesterol	Number	460	805
	Mean ± SD	5.3 ± 1.7	5.1 ± 2.0
	Median	4.9	4.8
	Range	2.8-14	2.0-17.4
Triglycerides	Number	460	821
	Mean ± SD	150.1 ± 62.8	204.1 ± 120.9
	Median	140	176
	Range	45-386	45-650

Comment:
The HDL cholesterol values were slightly lower in the qualified group (who were predominantly male), than in the nonqualified group. However, as per the above chart, there were subjects who qualified and did not qualify for the study who had very favorable total cholesterol/HDL ratios. There is no medical evidence that shows that subjects in this category would clinically benefit from taking a lovastatin drug.

The baseline HDL cholesterol tended to be higher in females than in males. Only 3 (3.4%) qualified females had an HDL < 35 compared with 91 (24.5%) males. Thirty-eight (42.7%) qualified females had an HDL > 60 compared with 36 (9.7%) males.

Of the 460 subjects who received study drug, 316 (68.7%) completed the study, returning for Visit 2. One hundred forty-four (31.3%) discontinued the study. The reasons subjects discontinued the study are shown in **Table 079-5.**

Table 079-5. Reasons Qualified Subjects Discontinued the Study

Reason	Number (%)
Clinical Adverse Event	39 (8.5)
Withdrew Consent	29 (6.3)
Lost to Follow-Up	29 (6.3)
Did Not Return for Visit 2	25 (5.4)
Did Not Complete Visit 2	6 (1.3)
Advice of Personal Physician	14 (3.0)
Advice of Study Physician	2 (0.4)

Comment: Almost a third of those who qualified for study medication did not complete the 8-week trial and this number does not take medication "compliance" into consideration.

Of the 460 subjects who received study medication, 128 (27.8%) did not have a Visit 2 lipid evaluation, and therefore did not complete the study. Of the 332 (78.2%) who did have the Visit 2 lipid evaluation, 39 fell outside the predefined day range for Visit 2. Of the remaining 293 subjects, 5 did not have an LDL cholesterol value due to triglyceride values > 400 mg/dl. Thus there were 288 (62.6%) subjects with a valid Visit 2 LDL value.

Three hundred sixty-three subjects were persistent with study medication of which 302 completed the study. The remaining 61 subjects failed to complete the study. Forty-seven subjects who were persistent, failed to have a Visit 2 lipid evaluation. The sponsor states that subjects could be persistent without having a Visit 2 evaluation for a number of reasons such as returning their study medication packaging through the mail. Of the 288 subjects with a valid LDL value, 280 were also persistent with study medication, and they represented the subject sample presented in the summarization of the relationship between compliance and efficacy.

Efficacy Results

After 8 weeks of therapy, the mean reduction in LDL cholesterol for the 460 subjects was 11.5%. The lower limit of the 95% confidence was not ≥ 14.7%. Thus, the sponsor states, it cannot be concluded that the subjects reached meaningful reduction in LDL cholesterol as specified in the protocol. However, when only those subjects with a valid Visit 2 LDL measurement were considered, the mean reduction was 18.4% and the upper limit of the confidence level was -16.4%. The sponsor states that this subset of subjects reached meaningful reductions of LDL according to the protocol.

Of the 293 subjects (see page 42) who had Visit 2 lipid testing within the predefined day range, the mean total cholesterol decreased 10.4% and the mean HDL increased 5.4%. Triglyceride values did not change consistently over the course of the study.

Comment: Subjects might have been following dietary and exercise recommendations provided by the study site, which could confound the results.

Persistence and Compliance Results

There were 363 (78.9%) subjects who were persistent (took drug at some time during the study). **Table 079-6** depicts the categories of compliance among the 363 subjects who were persistent.

Table 079-6. Categories of Compliance for the 363 Persistent Subjects

Category of Compliance	Number (%)
< 25%	26 (7.2)
25 to 49%	35 (9.6)
50 to 74%	37 (10.2)
75 to 100%	265 (73.0)

Comment: Seventy-three percent of subjects who took at least 1 tablet were compliant at least 75% of the time over the 8 weeks of the study. The reason for this low compliance is unknown.

Table 079-7 depicts the relationship between compliance and efficacy for those who had a valid LDL at Visit 2.

Table 079-7 (Sponsor's Table 28). Relationship of Compliance and Efficacy All Patients Who Were Persistent and Who Had a Valid LDL Value at Visit 2 (8 Weeks)

(N=280)

Quartile of Compliance	Mean Change (%) LDL Cholesterol Lovastatin 10 mg		
	N	Mean	Standard Deviation
<25 %	1	-37.96	
25 to 49%	5	-12.51	23.28
50 to 74%	17	-10.34	13.08
75 to 100%	257	-19.12	15.31

Comment: Although the table suggests that those in the highest compliance quartile had a 19.12% reduction of LDL cholesterol, the efficacy of other factors like diet and exercise were not considered. Again, whether a reduction of LDL in this population group is meaningful clinically, is unknown.

The sponsor determined that there was no significant relationship between age, gender, family history of heart disease, or baseline cholesterol levels (total and LDL) with persistence or compliance. Smokers were less likely to be persistent ($p = 0.037$) or be at least 75% compliant ($p = 0.004$).

The sponsor notes that 1149 participants self-reported that their total cholesterol was within the 190-250 mg/dl range and that, of these, 707 (61.5%) were correct.

Comment: If only 61.5% of consumers have accurate knowledge of their cholesterol, 39% might self-select incorrectly on that basis alone.

Safety:
Four subjects (0.9%) reported serious adverse events, none drug-related, and no subjects died. One hundred fourteen subjects (24.9%) had 1 or more adverse experiences and 79 subjects (17.2%) had drug-related adverse events. (See **Table 079-8.**)

Table 079-8. Adverse Experience Summary for the 460 Subjects Who Received Study Drug

Adverse Experience	**Number (%) subjects**
One or More	114 (24.8)
None	346 (75.2)
Drug-Related	79 (17.2)
Serious	4 (0.9)
Deaths	0
Discontinued Due to Adverse Event	39 (8.5)
Discontinued Due to Drug-Related Adverse Event	30 (6.5)
Discontinued Due to a Serious Adverse Event	2 (0.4)
Discontinued Due to Serious Drug-Related Adverse Event	0

Comment: Since 363 of the 460 subjects actually took the study drug, the percentage of those with drug-related side effects who used the medication is 21.7%. The percentage of those who discontinued due to a drug-related adverse event is 8.3%. This is higher than was seen in the efficacy trials (075, 016, 061).

The most common types of drug-related adverse experiences were those occurring in the digestive system 31 (8.5%), and nervous system/psychiatric 23 (6.3%) with flatulence 17 (4.6%) being the most frequently reported adverse event, followed by headache 15 (4.1%). (See **Table 079-9.**)

Comment: The denominator for these calculations is 363.

Table 079-9. Specific Possibly, Probably, or Definitely Drug-Related Adverse Experiences (Incidence ≥ 1%) by Body System (of the 363 Subjects Who Used Study Drug)

Adverse Experience	Number (%)
Body as a Whole/Site Unspecified	15 (4.1)
Asthenia/fatigue	6 (1.6)
Abdominal pain	5 (1.3)
Digestive	34 (9.4)
Flatulence	18 (5.0)
Acid Regurgitation, Reflux Esophagitis, Dyspepsia	6 (1.7)
Constipation	4 (1.1)
Musculoskeletal	16 (4.4)
Myalgia	5 (1.4)
Nervous System Psychiatric	23 (6.3)
Headache	15 (4.1)
Skin	10 (2.8)
Rash	4 (1.1)

Comment: Five subjects complained of myalgia; one had asthenia, but it is unclear if this was demonstrable muscle weakness. No CPK values were checked.

There were 4 subjects with serious clinical adverse experiences and these were considered not to be related to the drug. One subject, a 70 year old woman had a history of angina pectoris and was diagnosed with an acute subendocardial myocardial infarction while on the study drug. One subject, a 56-year-old male with a history of hypertension treated with 1 drug, underwent a routine physical examination, which revealed an abnormal stress test. He underwent 2-vessel coronary artery bypass surgery. A 73-year-old male was diagnosed with a myocardial infarction and was hospitalized for angioplasty. The fourth subject, a 62-year-old male with prostate cancer had a pelvic node biopsy that was positive for adenocarcinoma and was hospitalized for a pelvic lymph node dissection.

Comment: Despite the extensive telephone interview that asked about heart disease, angina, bypass surgery, and balloon angioplasty, and despite the specific warnings on the label, these subjects, who should have been under the care of a physician still were enrolled in this trial. This indicates that in the OTC market, many subjects with active coronary disease, a group to be excluded, would take this product

Thirty-nine subjects discontinued due to a clinical adverse experience. Three discontinued because of myalgias. Two subjects who discontinued reported that their symptoms (possibly, probably, or definitely related to lovastatin) persisted (that they had not recovered). One, with myalgia, asthenia and fatigue, was among the 3 who discontinued because of myalgias. The other subject complained of leg pain.

There were no laboratory safety evaluations performed nor were measurements of clinical or laboratory safety. There were no special examinations performed.

Summary: This study is based on the same unproved premise as the others, that healthy subjects can clinically benefit from taking lovastatin 10 mg chronically for cholesterol values in the stated range. This trial did not test the ability of subjects to self-select properly. The trial did demonstrate that subjects were poorly compliant, and that they often had an inaccurate knowledge of their cholesterol values.

The serious side effects in this trial were not thought to be caused by the study medication. Even with screening, 3 of the subjects with serious adverse events had serious coronary artery disease, and belonged in the care of a physician.

Conclusion: This study demonstrated that subjects have a poor knowledge of their actual cholesterol values and that compliance is a problem in this actual use setting. This protocol was poorly designed to provide robust efficacy data.

Protocol 081. A Multicenter, Open-Label, Storefront, Observational Use Study to Evaluate the Ability of Patients to Appropriately Self-Select Lovastatin 10 mg Utilizing an Enhanced label and Additional Label-Reinforcement Tools

Purpose:
The sponsors state that this study was designed to address medical concerns regarding unsupervised selection of lipid-lowering therapy in the traditional OTC open-shelf approach which permits unrestricted access to OTC medications. The sponsor notes from the pharmacy study (Protocol 076) that consumers need to be guided in relating their own medical history to the requirements of the proposed product label. The sponsor states that an enhanced back panel label was developed with greater emphasis on the lovastatin warnings and uses. A "starter kit" was also developed to increase the consumer's awareness of who is appropriate for lovastatin 10 mg.

Objectives:
1. To measure the effectiveness of the enhanced product label (via the appropriateness of self-selection) and label-reinforcement tools (via the eligibility of subjects still taking drug at Visit 2.
2. To examine the effectiveness of both the enhanced product label and label-reinforcement tools in 3 risk subsets from the population of ineligible subjects. Risk subsets included: (a) drug risk – drug interactions, premenopausal women, current liver disease, and allergy to MEVACOR™, (b) primary prevention patients – total cholesterol > 240 mg/dl only, and (c) high-cardiovascular risk – atherosclerotic heart disease, diabetes, stroke, or severe hypertension.
3. To evaluate the tolerability of lovastatin 10 mg as measured by the incidence of adverse experiences.

Investigators:
Fourteen nurse-co-investigators at 12 storefront study sites, and 1 physician at a toll-free number consultation center in the United States participated in this study.

Comment: The nurses in the study were registered nurses. The physician investigator was the same person as in the other actual use studies.

Study Design:
The open-label, uncontrolled, multicenter use study was conducted with an enhanced product label, a starter kit containing a videotape, and an incentive for patients to call a toll-free number where product specialists would help determine if the product was right for them. The sponsor states that the label was designed to highlight the warnings of the drug and the need to know cholesterol numbers. A marketing enhancement program was structured to reward subjects only if they availed themselves to the product specialists at the toll-free number. This trial consisted of 2 conceptual stages. The first stage was conducted in storefront clinical sites and was designed to determine the ability of participants to correctly self-select to purchase lovastatin 10 mg based solely on their understanding of the back-panel label, and knowledge of their medical history and total cholesterol value. The second stage of the study (beginning at the time of purchase and ending approximately 4 weeks thereafter) was designed to document the subjects' post-purchase behavior. Specifically, if they needed assistance with the label, whether they followed the label directions and called the toll-free label reinforcement service.

The subject recruitment advertising included television, radio and newspaper and, the sponsor states, was aimed at diverse socioeconomic and racial audiences. The copy was developed to attract middle aged and older individuals who had been unsuccessful in reducing cholesterol with diet alone. The advertisements indicated that callers must be men 40 years or older, or women at least 1 year past menopause. Callers could not have heart disease and must have known their total cholesterol was 200-240 mg/dl.

Comment: The "1 year past menopause" language (also used on the 081 "Red Arrow Label") differs from entry criteria for the other actual use studies which said, "55 years or older."

Exclusion Criteria at Telephone Appointment Stage:
1. Current or recent (within 2 months of study start) participation in any drug study.
2. Participation in any cholesterol-lowering study in the 2 years prior to study start (including a call to a study line for participation).
3. Participant was not able to read and understand English without assistance.
4. Participant or family member employed in a healthcare environment (i.e., physician's office, pharmacy, or pharmaceutical company).

Visit 1 (Day 1) – Initial Storefront Visit
Inclusion Criteria at Site (Visit 1)
1. Participants must have expressed interest in purchasing lovastatin 10 mg and paid for product.
2. Subjects must have signed an informed consent.
3. Subjects must have been able to comprehend and comply with study requirements.

All individuals who were interested in participating in the study and scheduled a storefront appointment were given a brief explanation of the self-selection part of the study and were given a product concept and the proposed over-the-counter label to read and refer to.

Comment: The "Red Arrow Label" had red arrows that pointed out warnings to the consumer. This label highlighted certain warnings in red ink and listed contraindicated concomitant drugs in both generic and proprietary names. Coumarin was not included.

Mibefradil dihydrochloride and HIV protease inhibitors were not listed on the label, but subjects taking these products were not permitted to participate in the study. Thus subjects on these medications were not afforded an appropriate opportunity to self-select.

This label, in a section entitled "additional warnings," had the statement, "Do not use Mevacor CC if you are taking more than 1 high blood pressure medication. This was the only study label with this warning.

The nurse co-investigator asked subjects to make a self-selection decision. They were asked if they (a) would like to buy the product right then, (b) were not at all interested in the product, or (c) need more information before they buy and use the product. Participants who answered, "Yes," to (a) paid the investigator $15 and were asked if they had any of the following 4 safety exclusions:

Exclusion Criteria at Site (Visit 1)

1. Allergy to prescription MEVACOR™
2. Active liver disease
3. Subjects currently taking mibefradil dihydrochloride, cyclosporine, itraconazole, ketoconazole (or other systemic azole antifungal medication), erythromycin, clarithromycin, nefazodone, gemfibrozil, niacin in doses > 500 mg/day, or an HIV protease inhibitor.
4. Women less than 1 year post menopausal

Subjects who acknowledged having any of these exclusions were ineligible to receive study drug; however, they were given a second chance to review the label and were allowed to examine the contents of the starter kit (as if they were at home). Label-reinforcement tools in the starter kit included an informational brochure, a videotape that stressed the safety warnings, a package insert, and a monetary incentive (gift certificate) to call a product specialist at a toll-free number who would review pertinent medical history and eligibility with the consumer. The gift certificate was for a free cholesterol test or a $15 check. The sponsor states that a similar incentive, perhaps in the form of a coupon for a free month of drug, would be used in the marketplace.

Participants were given the drug carton, including all of its contents (except the drug) at the storefront site. The investigator advised them to look over the contents of the carton and then asked them to make a repeat self-selection decision and give 1 of the following responses:

1. I want to begin to use the product.
2. I want to return the product and get my money back.
3. I do not want to use the product without getting more information.

Regardless of the decision, these participants were not allowed to receive drug. They were administered the medical history questionnaire, given a cholesterol pamphlet, reimbursed their $15 and given $10 compensation.

Participants who initially indicated that they needed more information before purchasing the product were asked to describe what information they needed. Anyone who indicated that they would like to first talk to the study doctor, the product specialist, or their own private physician did not receive study drug.

Anyone who indicated needing a cholesterol test was offered a free fingerstick lipid profile using the Cholestech L·D·X™ desktop analyzer. Subjects were given the test results, which were not part of the study database, and they were then asked to make a repeat self-selection decision. Participants who then indicated that they were interested in purchasing the product paid $15 to the nurse co-investigator. They were asked the safety exclusion questions and the same steps were followed as for those who originally indicated that they would like to purchase the product.

Participants who were not interested in purchasing lovastatin were asked to indicate the reason. Those who did not leave the study site with study drug at Visit 1 were administered a medical history questionnaire by the investigator. Participants who were not interested in the product were also asked the same safety questions as the ineligible participants. Ineligible participants who paid $15 for the study drug were reimbursed their money. All participants who did not receive study drug at Visit 1 were given $10 compensation for time and travel expenses.

Comment: The informed consent form for this study mentioned that research studies have shown that MEVACOR® was effective in slowing the development of atherosclerosis in middle-aged men with coronary heart disease. It does not tell the subjects that this effectiveness was not demonstrated in this patient population with lovastatin 10 mg. Unlike the informed consent for trial 076, which listed exclusions, this informed consent was less specific. In that regard it was less biasing and placed more of the self-selection decision on the individual's understanding of the label.

Eligible subjects received a 4-week (28-day) supply of open-label lovastatin 10 mg in a starter kit. Each carton of study drug contained a package insert, an informational videotape and brochure, a gift certificate, a wallet-sized "Mevacard" and reminder stickers. The subject was directed to take drug according to the label. The subject was given a Study Information Card, which included the days/times when the storefront was open, and the toll-free telephone number to consult with the study physician, ask any questions, or report adverse experiences. The "Mevacard" contained the product specialist and study physician telephone numbers and a reminder list of medications that should not be used with lovastatin 10 mg.

Comment: It is not clear if the sponsor is considering adding a videotape, brochure, and Mevacard to the medication package if sold OTC. The label reinforcement tools emphasized calling the toll-free number for assistance.

Phone Interview:
Subjects who called 1-888-LOWLDLC to receive their free offer were asked medical history questions using a telephone screening script, which represented the remaining inclusion/exclusion criteria.

Telephone Qualification – Inclusion Criteria
1. Men 40 years or older
2. Subjects who knew their total cholesterol value was 200-240 mg/dl

Comment: The Telephone Qualification Inclusion Criteria as listed in the electronic document did not mention the criteria for women. It is assumed that the criterion for women was 1-year post menopause (as on the product label for the study).

Telephone Qualification – Exclusion Criteria
1. Past history of liver disease
2. Currently taking any prescription cholesterol lowering medication or CHOLESTIN™
3. History of heart disease (heart attack or angina) or stroke.
4. Subjects taking more than 1 prescription antihypertensive agent.
5. Diabetes

Comment: A family history of coronary artery disease, especially prior to the age of 55 is a risk factor for myocardial infarction. Subjects with a positive family history of coronary artery disease, should have been excluded and urged to see their personal physicians.

They were automatically mailed a free American Heart Association cookbook. Subjects deemed appropriate for lovastatin 10 mg were advised to continue taking their study drug and bring any unused drug and all packaging to their scheduled follow-up and that, to confirm their eligibility, they would need a cholesterol test. They were advised that, to obtain accurate cholesterol readings, they should not eat any food for 6 hours prior to their appointment. They also received the $15 at Visit 2.

Subjects who were deemed inappropriate for lovastatin 10 mg were advised to stop taking study medication and to return their unused drug and packaging to the storefront site. They were told they would be refunded their $15 dollars at Visit 2. During the phone call, these subjects were advised to call their specific storefront to cancel their original appointment and schedule an earlier one. Unless a subject specifically requested a free cholesterol test after answering the medical history questions, he/she was not offered one. Those who indicated they would rather receive the free cholesterol test instead of the $15 refund, were allowed to receive the test at Visit 2. This procedure was

not part of the study; however, as specified at Visit 1, subjects were required to sign a release form acknowledging the minor discomfort of the fingerstick test.

Comment: It is not clear why the sponsor decided to exclude subjects taking 2 or more antihypertensive drugs and to include those taking 1 or those with untreated hypertension. Uncontrolled hypertension is a risk for coronary artery disease.

Follow-up Visit (Week 4)

At the follow-up visit, subjects returned any unused drug and empty (used) blister packs and cartons. The nurse counted the tablets and asked all subjects if they had taken drug within the past 48 hours. Those who had stopped taking the drug were asked to provide a reason (adverse experience; investigator determined the subject was inappropriate for drug treatment; other reasons (i.e., administrative, subject request). If subjects did not call to receive their free offer during the study, the nurse administered a medical history questionnaire. This included the same questions asked by the product specialist and given to ineligible participants at Visit 1. The nurse determined if the product was appropriate for the subject.

All those who elected to continue treatment in the extension protocol had a confirmatory lipid profile and those with a total cholesterol ≤ 240 mg/dl were allowed to continue. All subjects who did not enter the extension were given $20 compensation for time and travel expenses. Unsolicited clinical adverse experience information was collected by the nurse co-investigator or by telephone by the study physician or another nurse.

Comment: As with the other actual use trials, the case report forms did not ask subjects to list the medications they were currently taking. They were just given a list of contraindicated medications to check if they took, "yes" or "no". Only for the erythromycin –type and anti-fungal products were subjects offered a box to check if the "don't know". This would have been useful for all listed drugs. If subjects had to list, their medications we would have had a better opportunity to see if they accurately responded to the list of contraindicated medications.

Subjects who self-selected "Yes" at Visit 1, did not receive a cholesterol check until Visit 2 when they were deciding whether to enter the extension trial. At that point, they had already been taking lovastatin. Therefore, if their cholesterol met criteria for the continuation, ≤ 240 mg, we do not know how the treatment may have influenced the value.

A brief self-administered market research questionnaire was given to the following subjects to understand their reaction to the marketing materials at the conclusion of their participation in the study:

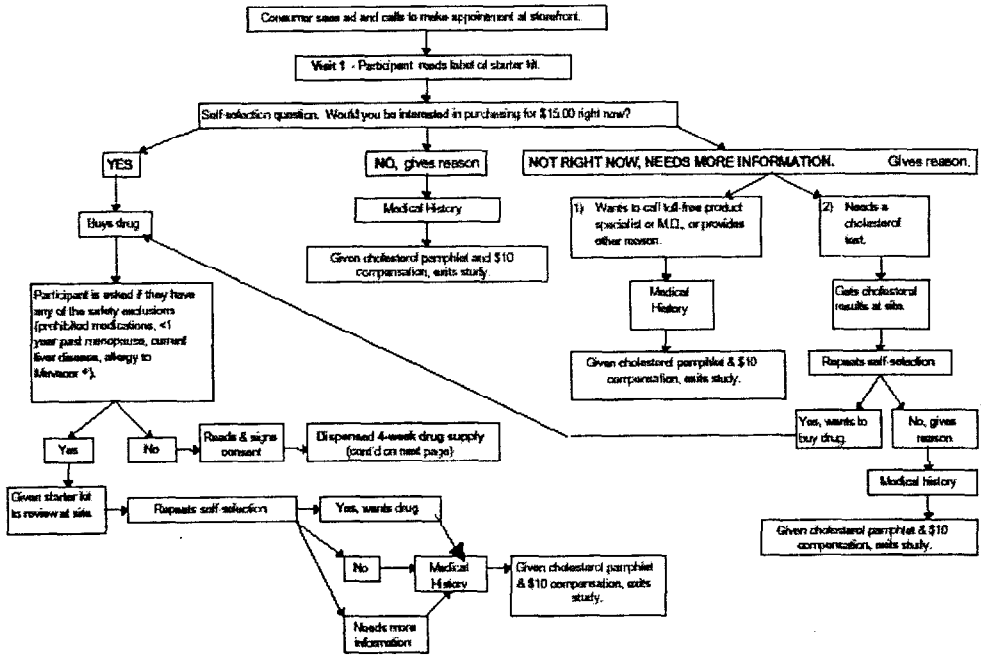
1. Those who had a safety exclusion at Visit 1 but still chose to buy the product after seeing the materials inside the carton.
2. Those who took product home and did not enter the extension.

Figure 081-1 summarized the study design for Protocol 081.

Study Design:

Figure 081-1. Study Design Flow Chart (in 2 parts)

Part I



Part II

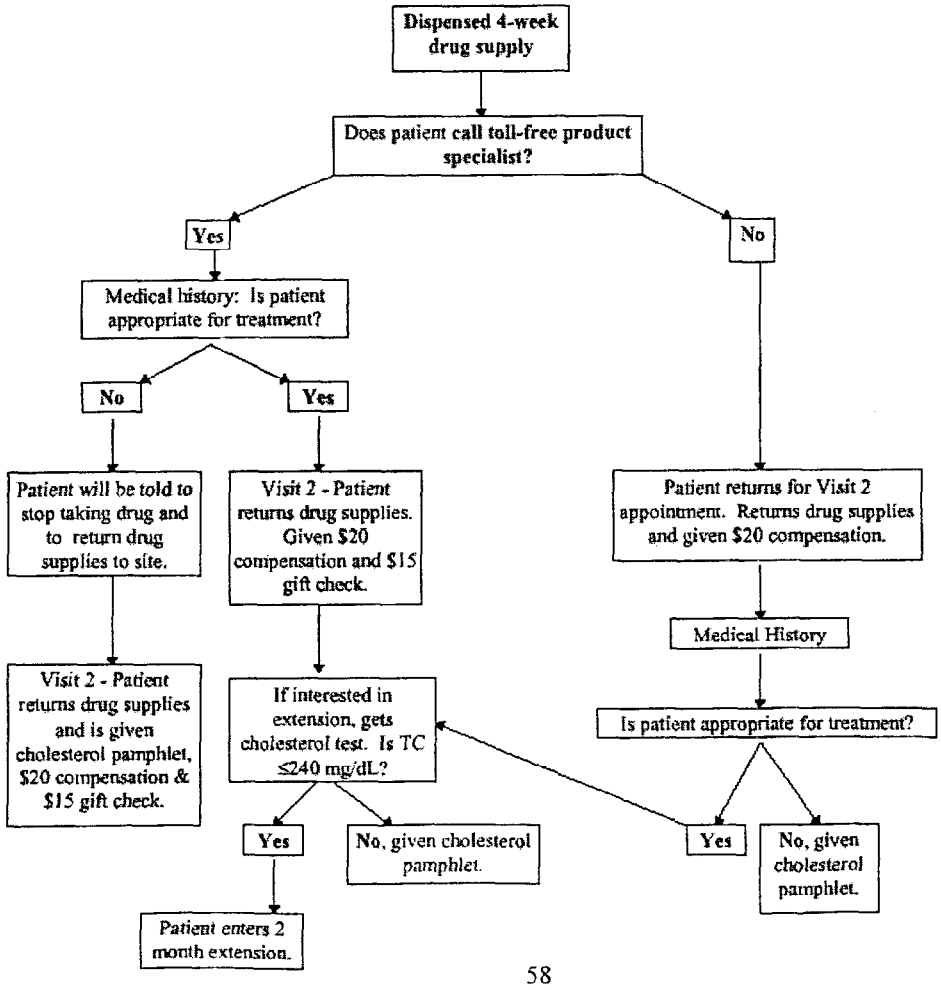


Table 081-1 is a flow chart of the clinical observations and laboratory measurements as they occurred during this study.

Table 081-1. Study Procedures Flow Chart

Activity	Visit 1 Day 1	Telephone Interview	Visit 2 Week 4
Subjects read concept and label and self-selected	X		
Lipid profile measured	X		
Subjects purchased study drug	X		
Participants were asked specific safety questions	X		
Ineligible participants reviewed contents of drug carton and made a repeat self-selection decision	X		
Eligible subjects signed informed consent	X		
Eligible participants received drug and information card	X		
Subjects may have called product specialist		X	
Collected returned drug			X
Collected adverse experiences			X
Subjects completed medical history	X		X
Subjects were compensated	X		X
Addendum consent to enter extension study			X

Comment: That the medical history was performed after subjects self-selected and that the informed consent did not emphasize exclusion criteria made this study less biased, than those described earlier in the review.

Evaluation Criteria
The following outcomes were collected for each participant and used to assess the effectiveness of the label and the label-reinforcement tools:
1. if an ineligible participant self-selected to purchase drug
2. if an ineligible participant maintained positive purchase decision after the simulated review of the "safety net" at Visit 1
3. if the participant called the product specialist after leaving the storefront site
4. if the subject was still on drug at Visit 2

Participants who were administered both the safety exclusion and the medical history questionnaires are referred to as participants with *known* eligibility since they had all of the available data to determine whether or not they were eligible. If a participant supplied partially completed questionnaires and the information indicated the participant was ineligible, the participant was counted as known and ineligible.

Ineligible subjects were classified into 4 risk subsets:
1. Safety risk – Currently taking nefazodone, cyclosporine, erythromycin, clarithromycin, ketoconazole, itraconazole, gemfibrozil >500 mg niacin; liver disease; allergy to lovastatin; a woman not > 1 year post menopause.

2. High cholesterol – self-reported total cholesterol > 240. A subset of this group are those subjects who self-reported high cholesterol as their only exclusion criteria (the primary prevention subset)
3. High cardiovascular – history of stroke, heart attack, diabetes; currently taking more than 1 antihypertensive medication
4. Other ineligible – males < 40 years old, past history of hepatitis or liver disease, self-reported total cholesterol < 200 mg/dl or unknown total cholesterol; currently taking CHOLESTIN™ or other cholesterol-lowering medication.

The self-selection "Yes" group were those who said they would purchase the product no matter whether they made this decision initially or after having a cholesterol test. The self-selection "No" group included those who said they wanted more information but no cholesterol test as well as those who would not buy the product. This group did not receive study drug.

Adverse experiences were rated as to severity:
1. Mild – Awareness of sign or symptom but easily tolerated
2. Moderate – Discomfort enough to cause interference with usual activity
3. Severe – Incapacitating, with inability to work or do usual activity

Drug relationship with adverse events were assessed.
1. Definitely not (no relationship)
2. Probably not (relationship is not likely)
3. Possibly (relationship may exist)
4. Probably (relationship is likely)
5. Definitely (unquestionable relationship)

There were no laboratory safety measurements in this study.

Statistical Analysis:
The study was planned to target approximately 3000 screened participants. Participants in the study were classified by their self-selection decision and by their eligibility for the OTC paradigm. As the study was designed, subjects who did not call the toll-free study number and did not return for Visit 2 were likely to have unknown eligibility.

A subject was considered to be "on drug at Visit 2" if he/she self-reported taking drug within the last 48 hours at the scheduled Visit 2. If a subject purchased drug and did not return for Visit 2, the sponsor considered the subject to be on drug at Visit 2.

Comment: It is unclear why the sponsor assumed a subject who was not compliant about returning for the second visit was compliant about taking the study medication.

Subjects who took all their medication were not counted as potentially successfully stopping drug. Thus, ineligible subjects who took all their drug prior to Visit 2 were not "on drug at Visit 2" but were still considered incorrect self-selectors.

All subjects who purchased lovastatin were included in the summary of adverse experiences. Any study participant who received drug but never returned for the follow-up visit was documented. The sponsor states that those who were lost to follow-up were assumed to have no adverse experiences.

Comment: The sponsor included subjects who never took the medication in their adverse events denominator. One cannot assume that those who were lost-to-follow up had no adverse events, since an adverse event may have precipitated a decision to drop out.

Results:
(See **Table 081-2**.) There were 2416 subjects who responded to study advertising and came to the clinic. One thousand fifteen (42.0%) of the 2416 screened participants self-selected "Yes" after reading the product label. Three hundred ninety-three participants wanted a cholesterol test before making a decision. Of these, 214 (54.5%) self-selected "Yes." Therefore, of all screened participants 1230 (50.9%) eventually self-selected "Yes" and 1187 (49.1%) self-selected "No."

Of those, 1230, 1144 received study drug. Thirty-eight (7.0%) of 86 subjects did not receive study drug because of safety risk (**Table 081-2**). Forty-eight did not receive drug because they did not give consent or withdrew it, could not comply or comprehend the study, and in one case, because of investigator error. Of the 1187 subjects who self-selected, "No", 903 (76.1%) needed more information.

Comment: The 38 did not receive study drug because they were either on prohibited medications, < 1-year post menopause, had current liver disease or a known allergy to Mevacor. It is unclear why 27 subjects withdrew consent and why 34 did not show for their final visits.

Of the 1144 who received the study drug the following should not have self-selected for the reasons listed:
1. *History of heart disease – 22 subjects*
2. *History of stroke/TIA – 14 subjects*
3. *Taking prescription drugs to lower cholesterol or other lipids – 41 subjects*
4. *Taking Cholestin – 4 subjects*
5. *Have hypertension – 211 (147 on medication)*
6. *History of hepatitis, liver disease, or other liver problem – 35 subjects*
7. *Drink alcohol – 462 subjects; 3 or more drinks most days – 26 subjects*
8. *Diabetes – 23 subjects*

Of the 1144 subjects who received drug, 851 (74.4%) completed the study. The reasons the remainder, 293, did not are listed in **Table 081-2.**

Comment: It is not clear why the 114 were considered to be inappropriate for lovastatin treatment.

Table 081-2. Subject Accounting

	Number
Self-Selected "Yes"	1230
Received Study Drug	1144 (100%)
Completed Study	851 (74.4%)
Discontinued Study	293 (25.6%)
Not Appropriate	114 (10%)
Adverse Experience	67 (5.9%)
Lost to Follow-up	48 (4.2%)
Returned Drug by Mail	34 (3.0%)
Withdrew Consent	27 (2.4%)
Did Not Complete Final Visit	2 (0%)
Did Not Receive Study Drug	86

Among the 1144 receiving drug, 321 (28.1) were females, 760 (66.4%) were males, and 63 (5.5%) had no gender recorded. The percentages were similar for the non-enrolled participants. Nine hundred two (78.8%) of those enrolled were Caucasian. A similar percent was noted for the non-enrolled. The age range among the enrolled ranged from 38-82 years for males and 41-96 years for females.

Comment: We cannot know with certainty that the women under 55 who enrolled were post-menopausal for > 1 year.

The sponsor had stated that the ads for the study were specifically designed to attract minority populations, specifically African Americans and Hispanics. The campaign was not very successful in this regard.

Of the 851 subjects who completed the study, a higher proportion was male 633 (74.4%).

Out of the 2264 total study participants with known eligibility (i.e., known medical history), 437 (19.3%) incorrectly self-selected (label alone did not work) after reading the label, and 244 (10.8%) were not caught by the label and the reinforcement tools (safety net). (See **Table 081.3**)

Of the 1112 subjects with known eligibility (i.e., known medical history) who self-selected "Yes" and actually would purchase lovastatin, 437 (39.3%) incorrectly self-selected after reading the label and 244 (21.9%) were not caught by the label and the reinforcement tools. (See **Table 081.3**.) The label reinforcements tools worked about half of the time to stop ineligible subjects, according to the label, from taking lovastatin 10 mg.

Of the 1112 purchasers with known eligibility, 176 (15.8%) were ineligible only for high self-reported cholesterol at Visit 1. Thirty-nine (3.5%) were ineligible because of safety risk. Eighty-three (7.5%) were ineligible and in the high cardiovascular risk group.

Table 081-3 presents the error rate out of all the participants who self-selected, "yes. The term "eligibility" in the table means that the medical history is known.

Table 081-3. Self-Selection Errors (Participants who were not appropriate for lovastatin 10 mg per label, but self-selected "Yes" to purchase)

Population	Label did not Work N (%)	Label and Reinforcement Tools did not work N (%)
Out of total study population (2264 subjects) with known eligibility	437 (19.3)	244 (10.8)
Out of 1112 who would purchase Lovastatin with known eligibility	437 (39.3)	244 (21.9)
Ineligible groups of the 1112 who would purchase Lovastatin (participants could be in more than 1 of the ineligible groups)		
Safety risk group	39 (3.5)	19 (1.7)
High cholesterol group	233 (21.0)	121 (10.9)
High cholesterol *only*	176 (15.8)	105 (9.4)
High cardiovascular risk group	83 (7.5)	44 (4.0)
Other ineligibles	184 (16.5)	89 (8.0)

Comment: The "other ineligibles" were those:

1. *who took prescription drugs to lower their cholesterol*
2. *with a history of liver disease, those who self-reported cholesterol <200*
3. *who were male and < 40 years of age*
4. *who did not know their total cholesterol level*
5. *who did not know if they were taking CHOLESTIN™.*

The sponsor states that 8 of the 39 subjects in the safety risk group did not have an opportunity to review the reinforcement tools in the post-purchase simulation and make a second decision due to investigator error. Of the 1187 subjects who self-selected "no," 81 (7%) were known to be in the safety risk group.

Comment: These numbers indicate that almost 40% of subjects might purchase lovastatin erroneously. The sponsor has not indicated how it would help subjects appropriately self-select in a drug store (i.e., if the reinforcement tools be immediately available to the consumer as through a video in the drug store). It is not known if the average consumer would take the time examine the reinforcement tools in the drug store setting before deciding whether to purchase the product.

Of subjects who received lovastatin with known eligibility (N=1043), 410 (39.3%) called the product specialist and 633 (60.7%) did not call. The proportion of ineligible subjects out of those who called 146 (35.6%) was comparable with the proportion for those who did not call 230 (36.3%). However, the proportion out of ineligible subjects who were

still on drug at Visit 2 or took all drug 56 (38.4%) for subjects who called was less than for subjects who did not call 169 (73.5%). See **Table 081-4.**

Table 081-4. Effectiveness of Toll-Free Number. Patients Who Received Drug with Known Eligibility (N=1043)

	Called Toll-Free Number N=410		Did not Call N=633	
	Eligible 264 (64.4%)	Ineligible 146 (35.6%)	Eligible 403 (63.7%)	Ineligible 230 (36.3%)
On drug at Visit 2 or took all drug	241 (91.3%)	56 (38.4%)	358 (88.8%)	169 (73.5%)
Not on drug at Visit 2 and did not take all drug	23 (8.7%)	90 (61.6%)	45 (11.2%)	61 (26.5%)

Comment: The difference of 36 percent indicates that the toll-free number worked to triage ineligibles off drug after purchase. In the OTC marketplace, depending on how much ready access subjects had to reinforcement tools, the availability of a toll-free number might assume even more importance. However, outside the protocol setting, it is unclear what percentage of subjects might actually use such a number.

In total there were 120 participants observed in the overall safety risk group. Of these, 83 (69.2%) were taking at least one interacting medication. (See **Table 081-5.**)

Table 081-5. Prevalence of Reasons for Participants in Drug Safety Exclusion

Safety Risk Categories*	**N (%)**	**Self-Selected "Yes" After Reading Label N (%)**	**Safety Risk Self-Selectors Who Participated in Simulation N (%)**
Overall # of Participants in Safety Risk Group	120 (100)	39 (33)	31 (79)
Interacting Medication	83 (69)	25 (30)	22 (88)
Less than 1 Year Postmenopausal	16 (13)	8 (50)	5 (63)
Current Liver Disease	14 (11)	5 (36)	4 (80)
Allergy to Lovastatin	8 (7)	1 (13)	0 (100)

*Participants might have had multiple reasons to be in safety risk. Participants also may have been taking multiple interacting medications.

After reading the label, 25 of the 83 (30.1%) self-selected, "yes," and 14 of these maintained their decision after simulation. Fifty-eight of the 83 (69.9%) self-selected, "no."

Fourteen participants reported current liver disease; thirteen were male. Five of the 14 self-selected, "yes," 2 of whom changed their mind after simulation. Eight (50%) of the 16 participants who were less than 1 year post menopausal, self-selected "yes" after reading the label. Five reviewed the simulation and 2 changed their self-selection status to "no." One of 8 subjects allergic to lovastatin self-selected, "yes." (See **Table 081-5.**)

Table 081-6 describes (in more detail) the number of participants taking medications known to interact with lovastatin, and their self-selection decisions after reading the label and after participation in the simulation.

Table 081-6. Number of Participants on Interacting Medications with Self-Selection Decisions (Participants may have been taking multiple interacting medications)

	Self-Selection "Yes" After Reading Label		Self-Selection "No" After Reading Label
	Maintained Decision After Simulation	Changed Decision After Simulation	
Medications	**N (%)**	**N (%)**	**N (%)**
Nefazodone (7)	1 (14.3)	1 (14.3)	5 (71.4)
Cyclosporine (1)	0	0	1 (100.0)
Erythromycin / Clarithromycin (12)	1 (8.3)	2 (16.7)	9 (75.0)
Ketoconazole/ Itraconazole (12)	5 (43.3)	0	7 (56.7)
Gemfibrozil (27)	2 (7.4)	3 (11.1)	22 (81.5)
Niacin (>500 mg/day) (27)*	5 (20.8)	2 (8.3)	17 (63.0)

* Three participants did not participate in the simulation. Proportions are based on 24 participants.

Table 081-7 lists the prevalence of participants in high cardiovascular risk categories.

Table 081-7. Participants in High Cardiovascular Categories (N=262)

Category	N (%)
Heart Attack History	65 (24.8%)
Stroke History	46 (17.6%)
Diabetes	101 (38.5%)
Hypertension (requiring more than 1 medication)	98 (37.4%)

Twenty-four (36.9%) with a history of heart attack self-selected, "yes." Of those with a stroke history, 15 (32.6%) self-selected, "yes." Twenty-six (25.7%) subjects with diabetes self-selected, "yes." Thirty-one (31.6%) subjects with hypertension and taking > 1 medication self-selected, "yes."

Among the 381 subjects in the subgroup of participants with **only** cholesterol >240 mg/dl, 176 (46.2%) self-selected, "yes."

Of the 255 subjects taking prescription drugs to lower their cholesterol level 23.9% self-selected, "yes." Forty-one (33.1%) of 124 subjects with a history of previous liver disease also self-selected inappropriately. Of the 102 participants with self-reported total cholesterol <200 mg/dl, 32 (31.4%) incorrectly self-selected. Of 18 males < 40 years old 4 incorrectly self-selected.

Comment: Across the safety risk categories, approximately 1/3 of subjects with risks inappropriately thought they could take the drug. This is unacceptable for the OTC marketplace. The implication is that either this study label was inadequate in terms of

the information given to consumers or written in such a way that consumers do not understand the risks. Another possibility is that this product is inherently too complicated for subjects to adequately understand how to use without the benefit of monitoring by a health care professional.

Drug inventory for subjects on drug at Visit 2 revealed that ineligible subjects took fewer tablets than eligible subjects. Of eligible subjects, 483 (92.5%) took 22-28 tablets whereas for the 180 ineligible subjects, 142 (78.9%) took 22-28 tablets. Two eligible subjects (0.4%) took 1-7 tablets, whereas 23 (12.8%) ineligible subjects took 1-7 tablets. Of the 187 ineligible subjects not on drug at Visit 2, 56 (29.9%) had taken no tablets and 45 (24.1%) had taken 1-7 tablets. Only 43 (23%) had taken as many as 22-28.

Table 081-8 summarizes why 187 ineligible subjects were not on drug at Visit 2.

Table 081-8. Reasons 187 Ineligible Subjects Were Not on Drug at Visit 2.

Reasons:	N (%)
Product specialist advised subject to stop	57 (30.5)
Product specialist advised subject not to start	28 (15.0)
Study doctor or personal doctor advised subject to stop	14 (7.5)
Study doctor or personal doctor advised subject not to start	14 (7.5)
Subject stopped on own	17 (9.1)
Subject decided on own not to take any tablets	11 (5.9)
Subject took all tablets	36 (19.3)
Other	10 (5.4)

Safety:

One thousand one hundred forty-four subjects received lovastatin 10 mg and were evaluated for safety. **Table 081-9** summarizes the clinical adverse experience for these subjects. There were 5 subjects who had an adverse experience that started in the primary study, but they did not discontinue the study until the treatment extension. They are not included in the table under the category "discontinued due to an adverse experience." The sponsor states that these subjects will be counted when the treatment extension data are summarized.

Table 081-9. Clinical Adverse Experience Summary For All 1144 Subjects Who Received Study Drug

Experience	N (%)
One or more adverse experiences	246 (21.5)
No adverse experience	898 (78.5)
Experiences determined by the investigator to be possibly, probably or definitely drug-related	169 (14.8)
Serious adverse experiences	6 (0.5)
Serious drug-related experiences	0
Deaths	1 (0.1)
Discontinued due to adverse experience	67 (5.9)
Discontinued due to drug-related experience	50 (4.4)
Discontinued due to serious adverse experience	5 (0.4)
Discontinued due to serious drug-related experience	0

Five of the 6 subjects with adverse experiences, none of which were drug-related discontinued the study because of the adverse experiences. The 6th subject died.

Comment: The subject who died did so as a result of trauma incurred during an automobile accident 21 days after enrolling in the study. The subject had received the study drug. The medical history was not performed on this subject.

The clinical adverse experiences with an incidence of 1% or more are summarized in **Table 081-10.**

Table 081-10. Number (%) of All 1144 Enrolled Subjects on Lovastatin with Clinical Adverse Events of ≥ 1% Incidence.

	N	(%)	Relation†
Subjects with one or more adverse experiences	246	(21.5)	169
Subjects with no adverse experience	898	(78.5)	
Body as a Whole/Site Unspecified	**43**	**(3.8)**	**31**
Pain, abdominal	18	(1.6)	13
Digestive	**89**	**(7.8)**	**74**
Diarrhea	22	(1.9)	18
Flatulence	27	(2.4)	27
Musculoskeletal	**62**	**(5.4)**	**40**
Myalgia	15	(1.3)	11
Nervous System/Psychiatric	**42**	**(3.7)**	**37**
Headache	25	(2.2)	25
Respiratory	**37**	**(3.2)**	**2**
Infection, respiratory, upper	13	(1.1)	0
Skin	**14**	**(1.2)**	**13**

† The numbers in this column are counts of subjects who had adverse experiences that were rated possibly, probably, or definitely drug related by the investigator.

Although a patient may have had two or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

All body systems are listed in which at least one patient had an adverse experience.

The most frequently reported adverse experience was flatulence 27 (2.4%), followed by headache 25 (2.2%) and diarrhea 22 (1.9%).

Of the 6 subjects with serious adverse experiences, none were considered to be related to the study drug. These subjects are described below.

1. Subject ID 01771 – This 51-year-old man was admitted to the hospital with an acute myocardial infarction and experienced associated ventricular arrythmias. His physician treated him with simvastatin and discontinued the study drug. He recovered from his acute illness.

Comment: This subject either did not know he had heart disease, or did not self-select properly.

2. Subject ID 06114 – This was a 73-year-old male with a history of labile hypertension, nondilated cardiomyopathy, chronic obstructive pulmonary disease, benign prostatic hyperplasia and squamous cell carcinoma of the left lung. He was hospitalized atrial flutter with a 2:1 AV block. He recovered from his acute illness.

Comment: This subject had multiple medical problems and should have been under the care of his physician. He took study medication despite the label warning about heart disease.

3. Subject ID 02841 – This 45-year old man died immediately from trauma suffered in a motor vehicle accident.

4. Subject ID 03921 – This 75-year-old woman with a history of asthma and chronic obstructive pulmonary disease was hospitalized with an exacerbation of her underlying condition and pneumonia. She recovered from her acute illness.

5. Subject ID 04297 – This was an 81-year-old man who was diagnosed with hepatic cancer. Pleurisy and a cardiovascular disorder are also mentioned. The investigator thought that the liver cancer was probably not related to having taken study drug.

6. Subject 08517 – This was a 62-year-old woman with a history of surgical bladder repair who was hospitalized for urolithiasis. She recovered from her acute illness.

Comment: It is clear that subjects with significant medical illnesses, who should be followed actively by a physician, were self-selecting to take this medication. None of these serious adverse events were likely to have been study drug related.

Fifty subjects (29.6%) of the 169 subjects with non-serious adverse events possibly, probably, or definitely drug related adverse experiences discontinued the primary study because of the adverse experience. These are listed in **Table 081-11.**

Table 081-11. Listing of 50 Subjects with Non-Serious Drug-Related Adverse Experiences Who Discontinued.

Gender	Age	Adverse Experience
Male	44	Headache, somnolence, dizziness, nausea
Male	48	Dyspepsia
Male	50	Diarrhea, myalgia
Male	43	Flatulence, dry mucous membranes, constipation, headache, anorexia, impotence
Male	52	Arthritis, muscle weakness, diarrhea, vomiting
Male	78	Breast pain, eye pain
Male	65	Diarrhea, myalgia
Male	46	Impotence
Male	44	Vertigo
Male	55	Dyspepsia, dizziness, acid regurgitation
Male	42	Abdominal pain
Male	66	Nervousness
Male	70	Diarrhea, headache
Male	45	Flatulence
Male	80	Vomiting
Male	42	Headache
Male	59	Rash
Male	60	Muscle cramp, diarrhea
Male	74	Nausea
Male	51	Fever
Male	52	Visual disturbance
Male	56	Tinnitus
Male	67	Muscle cramp, diarrhea
Male	54	Rash
Male	82	Rash
Male	44	Joint swelling, ankle pain
Male	51	Constipation
Male	59	Liver function abnormality
Male	47	Flatulence
Male	49	Headache
Male	62	Diarrhea
Male	51	Pain, dizziness, paresthesia
Male	56	Dyspepsia, constipation, acid regurgitation
Male	48	Pruritis, cough
Male	40	Foot and bone pain
Male	46	dyspepsia
Female	56	Myalgia, chest pain, acid regurgitation
Female	70	Vaginal bleeding
Female	55	Chest pain
Female	52	Abdominal pain, diarrhea
Female	57	Headache
Female	62	Flatulence, diarrhea
Female	73	Rash
Female	49	Arthralgia
Female	56	Headache, vomiting
Female	63	Rash
Female	46	Joint swelling
Female	75	Dizziness, asthenia/fatigue
Female	57	Myalgia
Female	64	Bone pain, headache, abdominal pain and distention

Comment: Fourteen (28.0%) of the subjects who discontinued due to an adverse event related to the drug were female and 36 (72%) were male. This is consistent with the enrolled percentages of males and females in the study. Some of the adverse events (such

as joint swelling and vaginal bleeding) that the investigators attributed to lovastatin may not have been related to it.

The 59-year-old man who withdrew because of what the sponsor calls "liver function abnormalities" had a medical history performed at visit 2. There was no answer recorded for question 5b ("Are you taking any of the following prescription medications for lowering lipids, cholesterol, or triglycerides?"). The subject was taking 1 drug for hypertension, and responded, "Yes," to questions 7, 8a, and 8b ("Have you ever had hepatitis, liver disease, or other liver problems? Do you typically drink alcoholic beverages, Do you typically drink 3 or more drinks on most days of the week?"). He did not respond to 8c, whether he called the study doctor or his personal physician to discuss taking Mevacor CC, yet, the reason given for stopping was that he was told to do so by the study doctor. No liver function tests were recorded on the case report form. He reported that his total cholesterol was 307 and that his LDL was 215. This is a subject who did not understand the study label and self-selected inappropriately. He returned 13 tablets.

The 5 subjects who developed an adverse experience in the primary study, but did not discontinue until the treatment extension are listed in **Table 081-12.** None of these adverse experiences were considered to be serious by the investigators.

Table 081-12. Five Subjects with Adverse Experiences in the Primary Study Who Discontinued During the Extension.

Gender	Age	Adverse Experience
Male	48	Impotence, dysuria
Male	69	Abdominal pain
Male	60	Headache
Male	53	Abdominal distention
Female	96	Weight gain

There were no laboratory safety evaluations performed in this trial nor were clinical safety measurements performed.

Comment: As with the other actual use trials, the sponsor chose not to perform liver enzymes, other liver function tests, or CPKs on the study participants. Therefore, the safety information presented in this actual use trial is incomplete.

Summary: Almost 40% of subjects in this trial self-selected inappropriately. It is unclear what impact the "safety-net" tools would have on the OTC consumer, i.e. whether they would buy the "refills" initially in lieu of the introductory package, which, with all of its added items, like a video, might cost more. This study did not evaluate laboratory work as part of the safety profile.

Conclusion: This protocol demonstrated that subjects have difficulty understanding if they can use lovastatin 10 mg based on the Red Arrow label. Subjects demonstrated an

inadequate knowledge of their cholesterol values and medical history. The safety information was incomplete.

DISCUSSION:
One objective of these 4 actual use trials was to demonstrate that consumers could appropriately self-select to use lovastatin 10 mg based on treatment guidelines established by the sponsor. It is yet not known whether people who comply with these treatment guidelines and lower their cholesterol can benefit clinically from taking lovastatin or, how many years of drug treatment would be needed to demonstrate such a benefit. The risk/benefit ratio of taking medication in this population is thus unknown.

The National Cholesterol Education Program (NCEP)[2] published recommendations for cholesterol management in 1993. Since these guidelines were published, many clinical trials including the Scandinavian Simvastatin Survival Study[3], the Cholesterol and Recurrent Events Trial[4,5], and the West of Scotland Coronary Prevention Study[6] have demonstrated their usefulness.

The NCEP recommendations acknowledge a spectrum of risk for CHD from high to low and place emphasis on that risk status as a guide to the type and intensity of cholesterol-lowering therapy. The risk categories are:

1. ***Those at highest risk for future CHD events because of prior CHD or other atherosclerotic disease***
2. ***Those without evident CHD who are at high risk because of high blood cholesterol together with multiple other CHD risk factors***
3. ***Those with high blood cholesterol but who are at low risk otherwise. This group especially young adult men (under 35 years of age) and premenopausal women.***

(See Attachment for specific published recommendations.)

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[7], a 5-year primary prevention trial using lovastatin, differed from previous primary prevention trials. (Reference provided in Attachment).
The FDA reviewed the AFCAPS/TexCAPS trial as part of NDA 19-643/labeling supplement 055. Subgroup analyses performed by the FDA revealed a significant reduction in the rate of combined primary events comprised of sudden death, fatal and nonfatal myocardial infarction, and unstable angina in lovastatin treated patients with ≥ 2 CHD risk factors across a range of LDL levels ≥ 130 mg/dl. Risk reduction was also demonstrated for the subgroup with HDL < 35 mg/dl. Results for women were only suggestive of benefit because the number of events for women was very low. There were too few events among those participants with age as their only risk factor in this study to adequately assess outcomes in this subgroup.

With regard to side effects, the medical reviewer noted that even though the incidence was rare (0.6%), clinically important elevations in hepatic transaminases as early as 12 weeks and as late as 5.2 years were seen. There were more participants in the lovastatin (110) than the placebo (70) group with drug-induced ALT elevations. This

difference was significant P=0.003. The reviewer recommended that clinicians who prescribe lovastatin periodically monitor their patients even after the first year of therapy. The sponsor did not present data to show that liver disease is not a problem on lovastatin 10 mg in the unmonitored OTC population.

Creatine phosphokinase (CPK) elevations > 10 times the upper limit of normal (ULN) were rare in the AFCAPS/TexCAPS trial and the incidence (0.7%) was the same between lovastatin 20 mg and 40 mg and placebo. There were no cases of drug-induced myopathy (defined as CPK > 10X ULN) and no discontinuations secondary to drug-induced myopathy. CPK measurements in subjects complaining of muscle aches or weakness were not performed in the actual use trials so we do not know whether myopathy was a concern in this self-selecting population.

In NDA 21-213 the sponsor is proposing drug treatment for cholesterol (lovastatin 10 mg) in an OTC population without CHD. The target population is designed to include healthy subjects who have fewer than 2 risk factors for CHD in addition to subjects who have ≥ 2 and the protocols use the cholesterol level as a surrogate marker for clinical benefit. This population does not meet the NCEP guidelines for drug therapy. The AFCAPS/TexCAPS trial, did not demonstrate significant clinical benefit for the < 2 CHD risk factor population who took lovastatin 20 mg or 40 mg. There is no proof that lowering cholesterol with lovastatin 10 mg in the proposed population would decrease the incidence of myocardial infarctions or strokes.

In the OTC marketplace subjects, with minimal risk of developing CHD, could choose to take lovastatin 10 mg and thereby place themselves at risk of side effects. The mean HDL in Protocol 076 was higher than for the AFCAPS/TexCAPS. Results of the Framingham Study indicate that the presence of important co-morbidity should temper the aggressiveness of cholesterol treatment, as should a markedly elevated HDL cholesterol.[8] An HDL cholesterol level below 35 mg/dl justifies more intense efforts to lower the LDL level (as might an elevated Lp(a)). Fuster V, Gotto AM, Libby P, et al., recommend tailoring therapy to the individual patient.[9]

In AFCAPS/TexCAPS, the compliance at approximately 6 months was close to 90%, but there was a steady decline to approximately 71% at the end of the study. Andrade SE, et al demonstrated a 15% 1-year probability of lovastatin discontinuation by patients in a health maintenance organization setting.[10] In the NDA 21-213 actual use trials, compliance was as follows:

1. *In Protocol 076, 27.6% of subjects discontinued during the first 24 weeks.*
2. *In Protocol 079, 31.3% of subjects discontinued the 8-week study.*
4. *In Protocol 081, 25.6% of subjects discontinued the 4-week study.*

This may imply that subjects who self-prescribe lovastatin 10 mg are not as compliant as subjects who receive their medication from and are followed by a physician.

Many subjects in 21-213 did not self-select properly with regard to whether they could take lovastatin. This was in large part because many did not have an accurate knowledge of their cholesterol values or of their concomitant medications. The

inadequacy of the labels for the 4 actual use protocols could have also contributed to self-selection error. None of the labels were in the FDA required "Drug Facts" format for OTC labeling.

The laboratory measurements in the actual use trials were performed on a desktop analyzer, and presumably, this is the way consumers would check their lipid values in a pharmacy when deciding whether to purchase lovastatin. Bachorik,[11] notes that the CHOLESTEC analyzer most accurately measures TC, HDL, and TG on whole blood, and that values obtained simultaneously from capillary (fingertip) and venous samples from individual patients can vary considerably. Desktop analyzers are fairly accurate on average, but measurements tend to be more variable than those obtained with laboratory methods.[11] Fingerstick specimens as well as the training of the personnel who operate the analyzers may contribute to this variability.[11]

The NCEP guidelines recommend a 9-12 hour fast, not a "2-hour fast." Because of variability in measurements, as per NCEP guidelines, and as was done in AFCAPS/TexCAPS, subjects should have had at least two blood samples analyzed for lipids to determine drug eligibility. If, realistically, OTC consumers would not comply with enough, properly fasted, cholesterol measurements to provide an accurate determination of their baseline cholesterol profiles, this would argue against the appropriateness of OTC self-diagnosis and treatment.

FINAL CONCLUSION:
The design and results of the actual use trials were inadequate in the following ways:

1. *Since the HDL value is an important determinant of risk for CHD, it should be included as a factor to determine who can take lovastatin 10 mg. Consumers should be tested to determine if they understand the meaning of their HDL level and can appropriately use this information as a factor in self-selection.*
2. *A single cholesterol test performed without a proper fast is a poor way to decide whether someone should take lovastatin 10 mg. The sponsor should demonstrate that proper screening methods and compliance can be achieved in the OTC setting.*
3. *The labels did not provide sufficient information to use the product effectively.*
4. *Self-selection errors were too frequent.*
5. *The safety information was incomplete because laboratory data (especially LFTs and CPKs) was not provided.*
6. *The compliance rate in the OTC setting was poor. This would probably impact on any long-term benefit to be derived from taking lovastatin 10 mg in this population.*
7. *A long-term clinical benefit of taking lovastatin 10 mg in the population at low risk for CHD (especially those with < 2 risk factors) has not been demonstrated.*

Unless these problems can be solved, lovastatin 10 mg should not be approved for OTC use.

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